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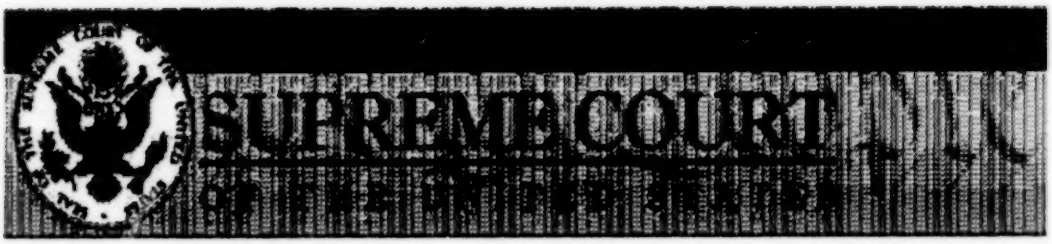

No. 13-854

Title:	Teva Pharmaceuticals USA, Inc., et al., Petitioners v. Sandoz, Inc., et al.
Docketed:	January 17, 2014
Linked with 13A458	
Lower Ct:	United States Court of Appeals for the Federal Circuit
Case Nos.:	(2012-1567, 2012-1568, 2012-1569, 2012-1570)
Decision Date:	July 26, 2013
Rehearing Denied:	October 18, 2013

Questions Presented

--- Date---	------- Proceedings and Orders----------
Nov 4 2013	Application (13A458) to recall and stay mandate pending the filing and disposition of a petition for a writ of certiorari, submitted to The Chief Justice.
Nov 5 2013	Response to the application (13A458) requested by The Chief Justice, due Tuesday, November 12, 2013, by 10 a.m.
Nov 12 2013	Response to application from respondent Sandoz, Inc., et al. filed.
Nov 13 2013	Reply of applicant Teva Pharmaceuticals USA, Inc., et al. filed.
Nov 13 2013	Application (13A458) denied by The Chief Justice.
Jan 16 2014	Petition for a writ of certiorari filed. (Response due February 18, 2014)
Feb 5 2014	Brief of respondents Sandoz, Inc., et al. in opposition filed.
Feb 19 2014	DISTRIBUTED for Conference of March 7, 2014.
Feb 26 2014	Reply of petitioners Teva Pharmaceuticals USA, Inc., et al. filed. (Distributed)
Mar 10 2014	DISTRIBUTED for Conference of March 21, 2014.
Mar 24 2014	DISTRIBUTED for Conference of March 28, 2014.
Mar 31 2014	Petition GRANTED.
Apr 4 2014	Application (13A1003) to recall and stay the mandate of the United States Court of Appeals for the Federal Circuit pending the sending down of the judgment of this Court, submitted to The Chief Justice.
Apr 8 2014	Response to the application (13A1003) to recall and stay the mandate requested by The Chief Justice. The response is due Monday, April 14, 2014, by 5 p.m.
Apr 14 2014	Response to application from respondents and motion for leave to file under seal declarations in support of respondents filed.
Apr 17 2014	Reply of applicant Teva Pharmaceuticals USA, Inc., et al. filed.
Apr 18 2014	Application (13A1003) denied by The Chief Justice. (In Chambers Opinion)

May 5 2014	The time to file the joint appendix and petitioners' brief on the merits is extended to and including June 13, 2014.
May 5 2014	The time to file respondents' brief on the merits is extended to and including August 11, 2014.
May 16 2014	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for respondents Mylan Pharmaceuticals, Inc., et al.
Jun 13 2014	Joint appendix filed. (Statement of costs filed.)
Jun 13 2014	Brief of petitioners Teva Pharmaceuticals USA, Inc., et al. filed.
Jun 13 2014	Motion for leave to file Volume 4 of the joint appendix under seal filed by petitioners Teva Pharmaceuticals USA, Inc., et al.
Jun 16 2014	Brief amicus curiae of the United States in support of neither party filed.
Jun 16 2014	Brief amicus curiae of Federation Internationale Des Conseils En Propriete Intellectuelle (FICPI) in support of neither party filed.
Jun 18 2014	Motion DISTRIBUTED for Conference of September 29, 2014.
Jun 20 2014	Brief amici curiae of Professors Peter S. Menell, et al. in support of neither party filed.
Jun 20 2014	Brief amicus curiae of Houston Intellectual Property Law Association in support of neither party filed.
Jun 20 2014	Brief amicus curiae of American Bar Association in support of neither party filed.
Jun 20 2014	Brief amicus curiae of Fresenius Kabi USA, LLC in support of neither party filed.
Jun 20 2014	Brief amicus curiae of American Intellectual Property Law Association in support of neither party filed.
Jun 20 2014	Brief amicus curiae of Intellectual Property Owners Association in support of neither party filed.
Jul 9 2014	Record requested from U.S.C.A. Federal Circuit.
Jul 18 2014	SET FOR ARGUMENT ON Wednesday, October 15, 2014
Jul 21 2014	Record received from U.S.D.C. Southern District of New York (3 Boxes), the records in this case are SEALED.
Jul 21 2014	Record received from U.S.C.A. Federal Circuit. The record is located on PACER, confidential documents are filed electronically.
Aug 11 2014	Brief of respondents Sandoz, Inc., et al. filed.
Aug 14 2014	CIRCULATED.
Aug 16 2014	Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.
Aug 18 2014	Brief amici curiae of Intel Corporation, et al. filed. (Distributed)
Aug 18 2014	Brief amici curiae of Google Inc., et al. filed. (Distributed)
Sep 10 2014	Reply of petitioners Teva Pharmaceuticals USA, Inc., et al. filed. (Distributed)
Oct 2 2014	Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED.
Oct 2 2014	Motion for leave to file Volume 4 of the joint appendix under seal GRANTED.
Oct 15 2014	Argued. For petitioners: William M. Jay, Washington, D. C. For United States, as amicus curiae: Ginger D. Anders, Assistant to the Solicitor General, Washington, D. C. For respondents: Carter G. Phillips, Washington, D. C.

PETITION FOR WRIT OF CERTIORARI

13- 854

No.

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Petition for a Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Rule 52(a) of the Federal Rules of Civil Procedure provides that in matters tried to a district court, the court's "[f]indings of fact must not be set aside unless clearly erroneous."

The question presented is as follows:

Whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel explicitly did in this case), or only for clear error, as Rule 52(a) requires.

PARTIES TO THE PROCEEDING

Petitioners are Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. All were plaintiffs-appellees below.

Respondents are Sandoz Inc., Momenta Pharmaceuticals Inc., Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. All were defendants-appellants below.

Sandoz International GmbH and Novartis AG were defendants in the district court, but were not parties in the court of appeals.

RULE 29.6 STATEMENT

The parent companies of Teva Pharmaceuticals USA, Inc. are: Orvet UK Unlimited, Teva Pharmaceutical Holdings Cooperative U.A., Ivax LLC (f/k/a IVAX Corporation), Teva Pharmaceuticals Europe, B.V., and Teva Pharmaceutical Industries Ltd.; Teva Pharmaceutical Industries Ltd. is the only publicly traded company that owns 10% or more of Teva Pharmaceuticals USA, Inc.

Teva Pharmaceutical Industries Ltd. has no parent company, and no publicly traded company owns 10% or more of Teva Pharmaceutical Industries Ltd.

The parent companies of Teva Neuroscience, Inc. are: IVAX Corporation, Teva Pharmaceuticals USA, Inc., Orvet UK Unlimited, Teva Pharmaceutical Holdings Cooperative U.A., Ivax LLC (f/k/a IVAX Corporation), Teva Pharmaceuticals Europe, B.V., and Teva Pharmaceutical Industries Ltd.; Teva Pharmaceutical Industries Ltd. is the only publicly

traded company that owns 10% or more of Teva Neuroscience, Inc.

Yeda Research and Development Co. Ltd. is wholly owned by Yeda Trust; no publicly traded company owns 10% or more of Yeda Research and Development Co. Ltd.

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PETITION FOR A WRIT OF CERTIORARI

Petitioners Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. (collectively "Teva"), respectfully petition for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The decision of the court of appeals (Pet. App. 1a-25a) is reported at 723 F.3d 1363. The district court's claim-construction decision (Pet. App. 26a-72a) is reported at 810 F Supp. 2d 578. A previous decision of the district court denying Sandoz's motion for summary judgment is reported at 749 F Supp. 2d 130.[1] The district court's post-trial findings of fact and conclusions of law are reported at 876 F Supp. 2d 295.

JURISDICTION

The judgment of the court of appeals was entered on July 26, 2013. Pet. App. 2a. A petition for rehearing was denied on October 18, 2013. *Id.* at 84a-85a. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

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[1] This petition uses "Sandoz" to denote respondents Sandoz Inc. and Momenta Pharmaceuticals Inc., and "Mylan" to denote respondents Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd.

STATUTORY PROVISION INVOLVED

Rule 52 of the Federal Rules of Civil Procedure provides in pertinent part:

Findings and conclusions by the court; judgment on partial findings

(a) FINDINGS AND CONCLUSIONS.

(1) *In General.* In an action tried on the facts without a jury or with an advisory jury, the court must find the facts specially and state its conclusions of law separately. The findings and conclusions may be stated on the record after the close of the evidence or may appear in an opinion or a memorandum of decision filed by the court. Judgment must be entered under Rule 58.

* * * *

(6) *Setting Aside the Findings.* Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility.

INTRODUCTION

This case concerns the Federal Circuit's longstanding unwillingness to apply in patent cases the standard of review that this Court has prescribed in the Federal Rules of Civil Procedure. "Findings of fact" made by a district court after a bench trial "must not be set aside unless clearly erroneous." Fed. R. Civ. P 52(a)(6). That standard applies whether those findings are "based on oral or other evidence," such as documentary or written evidence. *Id.* But the Federal Circuit will not apply that standard when

the findings are made in the course of patent interpretation. It reserves all such questions, no matter how fact-intensive, for itself to review *de novo*.

The Federal Circuit's disregard of the Federal Rules goes to a truly foundational question of patent litigation. District courts in patent litigation must construe the claims of a patent before trial—or even summary judgment proceedings—can take place. Both infringement and invalidity often depend on how the patent claims are construed. Yet no matter how much scientific evidence the district court hears, and no matter how fact-based its findings, the Federal Circuit will pay them no deference. That practice is contrary to Rule 52(a) and to this Court's decisions interpreting that Rule. It makes patent litigation longer, more expensive, and less predictable. And it asks appellate judges to make fact-intensive judgments that this Court has wisely left to trial judges. A growing number of Federal Circuit judges have concluded that the standard of review their court applies is flawed or simply wrong.[2] But thus far a majority of the Federal Circuit has insisted that this Court's decisions compel *de novo* review.

This case illustrates the danger of reviewing facts *de novo*. In this case the district court made express findings about certain historical and scientific facts, pertaining to the knowledge and understanding that

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[2] *See, e.g.*, *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 659 F.3d 1369, 1373 (Fed. Cir. 2011) (O'Malley, J., dissenting from denial of rehearing en banc); *id.* (Moore, J., dissenting from denial of rehearing en banc); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1040 (Fed. Cir. 2006) (Michel, C.J., dissenting from denial of rehearing en banc); *id.* at 1044 (Rader, J., dissenting from denial of rehearing en banc); *id.* at 1046 (Moore, J., dissenting from denial of rehearing en banc).

an expert in the field of polypeptide chemistry would have had in 1994. Those findings, in turn, guided the district court's interpretation of the key term of Teva's patents. The Federal Circuit did not review those findings for clear error; it reviewed them *de novo*, disagreed with them, and as a result construed the patent in a way that invalidated it. The standard of review determined the outcome.

This case therefore gives the Court an ideal opportunity to correct an important and fundamental error. The divisions within the Federal Circuit on this issue are deep and basic, stemming from disagreement over how to read this Court's decisions. While the Federal Circuit has tried to resolve it several times, and has another case before it presenting the question, a definitive answer—which the patent system urgently needs—can come only from this Court. If this Court does not address the issue in a case already pending on the merits this Term, it should not wait for another vehicle that may never arrive. The issue is squarely presented here, and the Court should take this opportunity to resolve it.

STATEMENT

A. The Federal Circuit Reviews Factual Findings *De Novo* When They Are Made During Claim Construction

The current system of reviewing factual issues *de novo* dates back to 1995. The en banc Federal Circuit acknowledged that it had previously been inconsistent: sometimes stating that claim construction may encompass factual issues, sometimes treating claim construction as a pure question of law. Henceforth, the court of appeals stated, it would treat eve-

ry aspect of claim construction, even the determination of historical facts, as a purely legal inquiry. *Markman v. Westview Instruments, Inc.* (*Markman I*), 52 F.3d 967, 976-77, 979 (Fed. Cir. 1995) (en banc). The Federal Circuit thought that its decision followed from various decisions of this Court, decided long before the adoption of the Federal Rules of Civil Procedure. The court of appeals read those cases as holding "that the construction of a patent claim is a matter of law exclusively for the court." *Id.* at 977. And because it saw "claim construction [a]s a matter of law," the court thought that factual findings underlying claim construction must be "reviewed *de novo* on appeal." *Id.* at 979. Several judges wrote separately to disagree with that standard of review. *Id.* at 989-98 (Mayer, J., concurring in the judgment); *id.* at 998-99 (Rader, J., concurring in the judgment); *id.* at 999-1026 (Newman, J., dissenting).

This Court granted certiorari in *Markman*, but did not address the standard of review for factual findings *by a district judge*. Instead, the Court examined whether the Seventh Amendment requires that factual issues underlying claim construction be resolved *by a jury*. *See* Pet. for Cert. at i, *Markman v. Westview Instruments, Inc.* (No. 95-26). The Court held that the Seventh Amendment imposes no such jury-trial requirement in this context. *Markman v. Westview Instruments, Inc.* (*Markman II*), 517 U.S. 370 (1996). But in answering the judge/jury question, it did *not* rule that claim construction is a question of law for all purposes. Rather, the Court noted that claim construction is "a mongrel practice," and it acknowledged that practice's "evidentiary underpinnings" even while holding that trial judges would do

a better job than juries of resolving those evidentiary issues in patent cases. *Id.* at 378, 390.

When it revisited the standard-of-review question, the en banc Federal Circuit concluded that it was doubly bound to review "any allegedly fact-based questions relating to claim construction" *de novo*. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). First, the court of appeals thought that this Court's decision in *Markman II* "conclusively and repeatedly" held that claim construction is purely legal. *Id.* at 1455-56. Second, although the court acknowledged that this Court "did not discuss the appellate standard of review," the court thought its own decision in *Markman I* was equally binding on that subject. *Id.* at 1456. Several judges again dissented vigorously.

The Federal Circuit took up the standard of review en banc a third time in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). This time, however, after receiving briefing and argument on the question whether deference is ever due to "any aspect of trial court claim construction rulings," the court of appeals "decided not to address that issue" and left its previous precedent, in *Markman I* and *Cybor*, "undisturbed." *Id.* at 1328. Two judges dissented.

Thus, all three en banc decisions on this subject over the last nineteen years produced the same result: in the context of claim construction, the Federal Circuit continues to review *de novo* even quintessentially factual rulings, such as findings reached after "live hearings with argument and testimony, sometimes covering several days." *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 659 F.3d

1369, 1374 (Fed. Cir. 2011) (O'Malley, J., dissenting from denial of rehearing en banc).

B. In This Case, The Federal Circuit Held Patent Claims "Insolubly Ambiguous" Despite A Trial-Court Finding That Skilled Artisans Would Understand Them

Teva is a pharmaceutical company that markets Copaxone®, a drug widely prescribed for the treatment of multiple sclerosis. Respondents are generic drug companies that sought FDA approval to market generic formulations of Copaxone®. Teva brought patent-infringement actions, later consolidated, against respondents in the Southern District of New York, contending that respondents' generic products would infringe various patents held by Teva.

1. The Patents Claim An Active Ingredient With Specific Molecular-Weight Characteristics

The active drug ingredient in Copaxone®, referred to as "copolymer-1," is a mixture of many different polypeptide chains made by joining together four amino acids in essentially random fashion. The individual polypeptide molecules that make up copolymer-1 vary in length, amino-acid sequence, and molecular weight. The patents in this case all reflect the inventors' discovery that, contrary to the prevailing understanding at the time, copolymer-1 promised therapeutic effectiveness against multiple sclerosis with an improved side-effect profile when the mixture contained polypeptide molecules of relatively *low* molecular weight.

The patent claims therefore refer to copolymer-1 with particular molecular weight characteristics. The claims at issue here describe the invention with reference to the *average* molecular weight of the polypeptide chains constituting the particular sample of copolymer-1. *E.g.*, Pet. App. 5a (quoting a claim that refers to "a molecular weight of about 5 to 9 kilodaltons").[3] The key question in the courts below was the meaning of "average molecular weight."

Several of the patents-in-suit contain the disputed claim term. The claim most relevant for this Court's purposes is the single claim of U.S. Patent No. 5,800,808, the last of the patents-in-suit to expire. Contrary to the Federal Circuit's incorrect statement (Pet. App. 24a n.5), the '808 patent expires in September 2015. *See id.* at 80a-81a.

2. Relying On Expert Evidence, The District Court Finds That The Patent Claims Are Not "Insolubly Ambiguous"

Respondents asserted various invalidity defenses. As relevant here, they contended that the term "average molecular weight" was "insolubly ambiguous," and that the patent claims containing that phrase were invalid for failure to satisfy the Patent Act's requirement that a patent be "definite" enough to be understood by "one skilled in the art." *E.g.*, *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001); *see* 35 U.S.C. § 112 ¶ 2

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[3] Some of what the panel called the "Group I" claims refer to "average molecular weight" and others to copolymer-1 having "a molecular weight," but it is undisputed that in the context of the Group I claims, "molecular weight" refers to *average* molecular weight. *See, e.g.*, Pet. App. 41a, 62a n.10.

(2006).[4] At the time of the invention, there were several methods of characterizing the average molecular weight of a sample of polypeptide molecules known to persons of ordinary skill in the art. *See* Pet. App. 4a-5a, 41a. Because the patent did not expressly specify one of those methods, respondents contended that a person of ordinary skill in the art could not discern which method the inventors meant.

The parties all recognized that the question turned on how a person of ordinary skill in the art would understand the term "average molecular weight" at the time of the invention. As the district court found and respondents' own experts largely agreed, "[t]he level of ordinary skill in the art in this case is very high." 876 F. Supp. 2d at 328-29. The parties submitted extensive evidence in the form of expert declarations, party documents, and deposition testimony.

The district court construed the claims and rejected respondents' contention that "average molecular weight" was insolubly ambiguous. Pet. App. 40a-62a. The court made extensive factual findings about what a person of ordinary skill in the art would have discerned from the patents and their prosecution histories. In making those findings, the district court found critically important the extensive testimony of Teva's expert witness, Dr. Gregory A. Grant. *See id.* at 42a-45a, 48a-50a, 52a.

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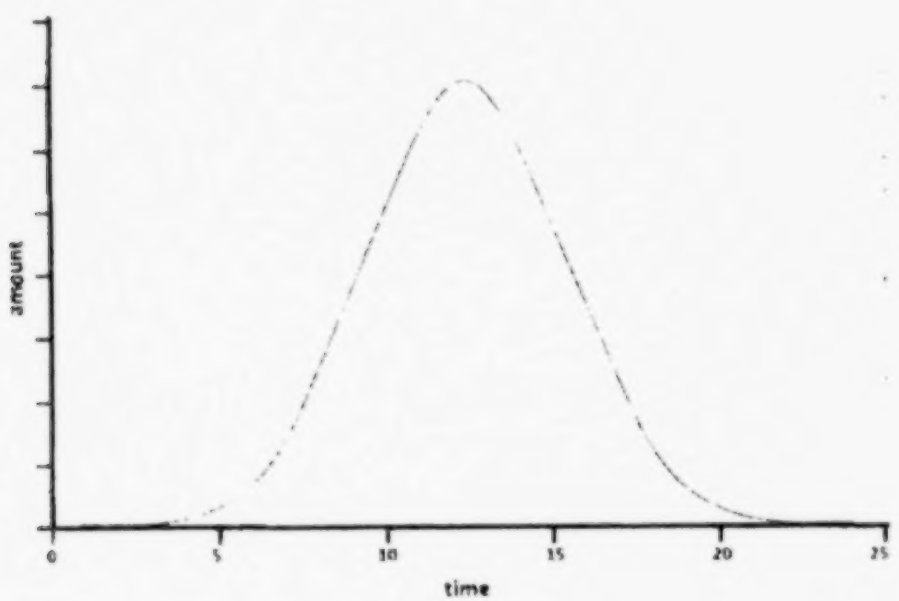
[4] Congress amended Section 112 in 2011 in ways not material here. The amendments do not apply to this case because it involves patents issued before September 16, 2012. *See* 35 U.S.C. § 112 note (Supp. V 2011). References in this petition to Title 35 are to the pre-2011 version.

While the patents did not specify which particular method for calculating average molecular weight was to be used, they *did* indicate that average molecular weight was to be determined using size exclusion chromatography ("SEC") technology to measure the proportions of a sample of copolymer-1 made up of polypeptide molecules of particular molecular weights. Pet. App. 42a-43a. The specified use of SEC technology was crucial to Dr. Grant's analysis.

SEC technology separates molecules in a sample on the basis of their size by passing the sample through a column filled with gel particles. Larger (and therefore heavier) molecules bypass the gel particles and thus travel through the column more quickly. By measuring the amount of the sample passing through the column at particular times, the user can determine the distribution of molecules in the sample. *Id.* at 107a-111a. By plotting those amounts against time, the user derives a "chromatogram," a graph that represents the amount of material that exits the column over time:

Chromatogram



C.A. App. 56292. The molecular weight associated with the highest point on a chromatogram reflects the "peak average molecular weight" or "M_p"—the molecular weight of the molecules present in the sample in greatest abundance.

M_p is the *only* expression of average molecular weight that can be derived directly from the chromatogram without the need for further calculations based on the underlying data. And none of the patents specifies any such further calculations. Therefore, Dr. Grant testified, a person of ordinary skill in the art would conclude that in the context of these patents, average molecular weight means M_p. To determine the average molecular weight with reference to other methods identified by respondents would require data manipulations that are nowhere suggested by the patents. *Id.* at 125a. Indeed, Dr. Grant pointed out, during the prosecution of one of the patents-in-suit Teva had stated unequivocally that average molecular weight was peak molecular weight. *Id.* at 129a. That was "the only statement that defined [average molecular weight] directly" in the prosecution history. *Id.* at 52a.

Respondents countered with testimony they had elicited when they cross-examined Dr. Grant at deposition. One set of respondents also submitted its own contrary expert testimony. They pointed to what they characterized as inconsistent statements made during the prosecution of other patents and anomalies in the figures set forth in the patents themselves. Pet. App. 48a-51a. But Dr. Grant addressed every one of these points. *See id.* at 48a-52a.

The District Court expressly "credited" Dr. Grant's explanation of the inferences that a Ph.D. experi-

enced in characterizing synthetic peptides would and would not have drawn from the patents and their file histories at the time of the invention, based on his or her extensive scientific knowledge. Pet. App. 49a, 50a, 52a. Based on that testimony, the District Court found that "average molecular weight" meant "peak molecular weight," and denied respondents' motions for summary judgment that the patents were indefinite. *Id.* at 62a.

Respondents proffered no additional evidence on the meaning of "average molecular weight" at the trial. Finding that respondents had failed to prove their indefiniteness defense by clear and convincing evidence, the district court entered judgment that the patents were not invalid. Pet. App. 76a-78a. The district court also held that respondents' generic products would infringe the patents, and it enjoined respondents from committing any such infringement during the remaining life of the patents. *Id.* at 76a-81a.

3. The Federal Circuit Reads The Patent Claims *De Novo* And Finds Them Insolubly Ambiguous

On appeal, respondents made no attempt to argue that the District Court clearly erred in finding that a person of ordinary skill in the art would read the patent claims to refer to "peak average molecular weight." Rather, they asked the Federal Circuit to consider *de novo* whether the patent claims were insolubly ambiguous.

The court of appeals reversed the district court and held the claims containing the term "average molecu-

lar weight" invalid as indefinite. Pet. App. 1a-25a.[5] The court expressly stated that it would not defer to the district court's factual findings: "On *de novo* review of the district court's indefiniteness holding, we conclude that Dr. Grant's testimony does not save [the pertinent] claims from indefiniteness." *Id.* at 10a; *accord id.* at 7a. Less persuaded by Dr. Grant's testimony than the district court, the panel concluded that a person of ordinary skill would be unable to discern the meaning of "average molecular weight" as used in the patents-in-suit.

Although both Dr. Grant and the district court had dealt with every one of the grounds on which the panel disagreed with Dr. Grant's reading of the patent, the panel gave no weight to the district court's contrary findings.

- The panel emphasized that other measures of average molecular weight—M_n and M_w—"can also be obtained from the data generated by the SEC method after some calculations." Pet. App. 10a. The panel did not acknowledge the key basis for the district court's finding—that the patent disclosed no such calculations, and M_p was the only measure that could be read directly from a chromatogram "*without* any further calculation." *Id.* at 43a, 48a (emphasis added).
- The panel found significant that the value the patent assigned to average molecular

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[5] The court of appeals rejected respondents' challenges to the infringement finding and their arguments that the remaining claims were invalid (except that the court miscategorized four claims as Group I claims rather than valid Group II claims). *See* Pet. App. 3a nn.1-2, 12a-24a; Pet. for Reh'g 13-15.

weight, in Example 1, was not at the peak of the graph in the patent, Figure 1. *Id.* at 10a-11a. The panel did not acknowledge or refute the District Court's finding, based on Dr. Grant's testimony, that the seeming discrepancy was merely a technical artifact: "the process of transferring the data from the chromatogram would likely cause the peak on each curve to shift slightly." *Id.* at 45a (quoting *id.* at 127a).

- The panel considered a statement in the prosecution history to be inconsistent with Teva's position. *Id.* at 9a-10a. But the panel did not acknowledge the District Court's finding, based on Dr. Grant's testimony, that no skilled artisan would have credited that statement as a possible expression of the meaning of "average molecular weight," because any skilled artisan would have known as a scientific matter that the statement was simply erroneous. *Id.* at 52a (citing *id.* at 128a-29a).

4. The Federal Circuit Declines To Hold Its Mandate.

While the appeal was under submission, the Federal Circuit ordered rehearing en banc in *Lighting Ballast Control LLC v. Philips Electronics North America Corp.*, 500 F. App'x 951 (2013) (No. 2012-1014). The question presented in *Lighting Ballast* is whether the Federal Circuit should overrule its precedent requiring *de novo* review of findings of historical fact when they are made in connection with claim construction.

Teva sought rehearing, noting that this case presented the same question already being considered en banc. Teva suggested deferring action or holding the mandate until *Lighting Ballast* is decided. Pet. for Reh'g 12-13. The court of appeals denied rehearing, Pet. App. 84a, denied a stay of the mandate, *id.* at 84a-85a, and issued its mandate the same day. The Circuit Justice declined to recall the mandate. No. 13A458.

REASONS FOR GRANTING THE WRIT

Claim construction takes place in virtually every patent litigation, and is "the single most important event" during each such case, because it "is often the difference between infringement and non-infringement, or validity and invalidity." *Retractable*, 659 F.3d at 1370 (Moore, J., joined by Rader, C.J., dissenting from denial of rehearing en banc). The standard by which the national court for patent appeals reviews the factual findings made by district courts in the course of those critical claim-construction decisions is plainly a question that should be settled. And Rule 52(a)(6) should settle it: "Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous
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But the proper standard of review is anything but settled. For more than 15 years, a majority of the Federal Circuit has declined to apply Rule 52(a)(6) and instead has applied the fundamentally flawed view that it must review all aspects of district-court claim constructions *de novo*, even the underlying factual findings. Three times since 1995, the Federal Circuit has ruled that it reviews facts found in claim

construction *de novo*. Each time, a determined minority has continued to object. And all the while, the Federal Circuit's wrongheaded rule has imposed billions of dollars in litigation costs on patentees and infringement defendants alike, who must litigate to final judgment in district court, only to be sent back for new proceedings once the Federal Circuit reverses the claim construction based on its own reading of the underlying factual record. It is time for this Court to bring the debate to a close and hold that factual findings in patent cases are entitled to the same measure of deference on appeal as factual findings in all other cases.

This case presents an excellent vehicle to decide that eminently cert-worthy question now. The flaws of *de novo* review are on prominent display in this case: the district court took evidence from all sides and devoted considerable time to understanding the science and the invention. The court of appeals undid that effort based purely on its own oversimplified reading of the record *de novo*. This case well illustrates why the detailed work of deciding the facts belongs to the district court.

I. The Federal Circuit's *De Novo* Approach Ignores The Applicable Federal Rule And Misapplies This Court's Precedent

The standard of review of findings of historical fact, like the ones the district court made here, is not up to the Federal Circuit. This Court and Congress have already prescribed it: since the merger of law and equity, every federal appellate court has been barred from setting aside "[f]indings of fact" unless they are "clearly erroneous." Fed. R. Civ. P. 52(a)(6).

The Federal Circuit has never attempted to square its precedent with the Rule, which is sufficient to dispose of the standard-of-review question here. That is just the sort of incorrect holding by the Federal Circuit—asserting that a generally applicable principle of law does not apply in patent cases—that this Court has often granted certiorari to correct.[6]

Indeed, the question presented here is, if anything, *more* fundamental and *more* important than many of those the Court has reviewed from the Federal Circuit in recent Terms. Almost *every* patent-infringement case involves claim construction, and the standard of review potentially affects almost every patent appeal from a district court to the Federal Circuit—more than 400 cases per year, many of them with multimillion- or billion-dollar sums potentially at stake.[7]

A. Rule 52(a) Applies To All Bench Trials

Rule 52(a) was drafted to apply to "*all* actions tried upon the facts without a jury." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 394-95 (1948) (emphasis added). The bench trial and claim-construction proceedings in this case were no exception. Indeed, as this Court has said, "Rule 52(a) *does not make exceptions* or purport to exclude certain categories of factual findings from the obligation of a court of appeals to accept a district court's findings unless clear-

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[6] *See, e.g., eBay v. MercExchange, LLC*, 547 U.S. 388, 394 (2006) (general principles governing injunctive relief in federal courts apply in patent cases); *Dickinson v. Zurko*, 527 U.S. 150, 165 (1999) (general principles governing review of agency actions apply to review of Patent Office decisions).

[7] See http://www.cafc.uscourts.gov/images/stories/Statistics/patent%20filings%20historical.pdf.

ly erroneous." *Pullman-Standard Co. v. Swint*, 456 U.S. 273, 287 (1982) (emphasis added). This Court has the power to make such exceptions for patent cases if it chooses; so does Congress. Neither has done so.

In its two leading decisions, *Markman I* and *Cybor*, the court did not even cite Rule 52(a), even though separate opinions cogently pointed out the conflict between that Rule and the court's standard of review. *Markman I*, 52 F.3d at 991 (Mayer, J., concurring in the judgment); *see also Cybor*, 138 F.3d at 1464 (Mayer, J., concurring in the judgment). Rather, the Federal Circuit has brushed off the restrictions on appellate review of factfinding by asserting that there *is* no factfinding in claim construction. *See, e.g., Cybor*, 138 F.3d at 1456 ("[A]s a purely legal question, we review claim construction de novo on appeal including any allegedly fact-based questions relating to claim construction."). The Federal Circuit insists that factfinding has no place in "document construction." *Id.* (quoting *Markman II*, 517 U.S. at 389). Respondents have echoed that position as well. *See* Resps.' Opp. to Stay Appl., No. 13A458, at 10-11. That view is plainly mistaken.

B. Patent Claim Construction Entails Finding Historical Facts

Judges construing patents often must establish a baseline of scientific, historical, or technical facts before beginning to interpret the document, precisely because patents are not written primarily for judges or lawyers. The principal function of a patent's *claims* is to provide public notice as to what technology may not be practiced without a license from the

patentee. *See, e.g.*, *Markman II*, 517 U.S. at 373; *Universal Oil Prods. Co. v. Globe Oil & Ref. Co.*, 322 U.S. 471, 484 (1944). These public disclosures are specifically directed to practitioners of the relevant scientific art. Accordingly, understanding and construing the patent requires understanding the perspective of a person of ordinary skill in the relevant art, at the time the patent was submitted.

A generalist judge seeking to understand and apply the skilled artisan's perspective must find *as a matter of fact* what the artisan knows. In this case, for example, the judge needed to consider: What was the level of ordinary skill in the art at the relevant time? *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) (describing "the level of ordinary skill in the pertinent art" as "basic factual inquir[y]"). (In this case, it required a Ph.D. and significant experience in the characterization of synthetic peptides. 876 F Supp. 2d at 328-29.) What did a skilled artisan know about the different ways to characterize the average molecular weight of polypeptide mixtures? Which of those measures may be read directly from a chromatogram, and which require further mathematical analysis?

These are manifestly questions of fact, not law. Similar questions of fact arise in most patent cases. Frequently the parties will contest these facts and require the trial judge to weigh conflicting evidence and assess the credibility of witnesses, often scientists, who disagree with each other.

This Court has long recognized that the answers to questions like these are factual findings, even when they are made in order to help interpret a legal document. In a contract case, for example, "extrinsic ev-

idence may be necessary to determine the meaning of words appearing in the document. This is true where technical words or phrases not commonly understood are employed " *Great N. Ry. Co. v. Merchants' Elevator Co.*, 259 U.S. 285, 291-92 (1922). The construction of a contract is undoubtedly a question of law. But "the function of construction is necessarily preceded by the determination of the matter of fact." *Id.* at 292.

The same is true in patent cases. This Court in *Markman II* recognized that claim construction is often a "mongrel practice (like construing a term of art following receipt of evidence)." 517 U.S. at 378. The decision in *Markman II* held that the various aspects of that "mongrel practice" were best performed by the district court, not the jury. But that holding says nothing about the role of the *appellate* court. The Federal Rule "easily" answers the latter question: when the court makes findings about the "evidentiary underpinnings" of claim construction, *id.* at 390, Rule 52(a)(6) requires deferential review. U.S. Amicus Br. at 9, *Lighting Ballast*, No. 2012-1014 (Fed. Cir. June 7, 2013).

Allowing district courts to play that role capitalizes on the "institutional advantages" that district courts have over appellate courts in this context. *Cybor*, 138 F.3d at 1478 (separate opinion of Rader, J.). "Trial judges can spend hundreds of hours reading and rereading all kinds of source material, receiving tutorials on technology from leading scientists, formally questioning technical experts and testing their understanding against that of various experts, [and] examining on site the operation of the principles of the claimed invention " *Id.* at 1477. By contrast,

"[a]n appellate court has none of these advantages": it holds parties to "strict time and page limits in oral and written presentations," and it receives only "a sterile written record [that] can never convey all the nuances and intangibles of the decisional process." *Id.* at 1477-78. Where district courts can spend "several days," an appellate court has only "mere minutes to devote to live exchanges with counsel." *Retractable*, 659 F.3d at 1374 (O'Malley, J., dissenting from denial of rehearing en banc).

C. A Growing Consensus Is Calling For Factual Findings In Claim Construction To Receive Due Deference

Numerous members of the Federal Circuit have repeatedly called for the court to overrule its practice of reviewing factual findings *de novo*. *See* pp. 4-7 & n.2, *supra*. The federal government has recently done the same. So have numerous other amici in *Lighting Ballast*. That broad agreement that the Federal Circuit is wrong underscores the need for review by this Court.

Now-Chief Judge Rader of the Federal Circuit has previously explained how the Federal Circuit's *de novo* treatment of factual findings aggravates the already-high cost of patent litigation. "The meaning of a claim is not certain (and the parties are not prepared to settle) until nearly the last step in the process—decision by the Federal Circuit." *Cybor*, 138 F.3d at 1476 (separate opinion of Rader, J.). In turn, "the focus shifts from litigating for the correct claim construction to preserving ways to compel reversal on appeal," and "the uncertainty, cost, and duration of patent litigation only increase." *Id.* Be-

cause patent litigation already "costs upwards of $15 billion per year to patentees and accused infringers," J. Jonas Anderson, *Secret Inventions*, 26 Berkeley Tech. L.J. 917, 952 (2011), the unnecessary relitigation that the Federal Circuit's rule requires potentially costs billions.

De novo review is all the more pernicious because it generally occurs late in the process, after discovery and trial. The Federal Circuit has the authority to entertain interlocutory appeals where (*inter alia*) reversal may "materially advance the ultimate termination of the litigation"—for example, where reversing the claim construction would leave no need for a trial. 28 U.S.C. § 1292(b) (2006); *see id.* § 1292(c)(1). But in its first 27 years, the Federal Circuit apparently granted interlocutory review of claim construction only *once*. *See Portney v. CIBA Vision Corp.*, 401 F App'x 526, 529 (Fed. Cir. 2010) (identifying a "peculiar" 2007 case as "the only occasion in which" the Federal Circuit entertained an interlocutory claim-construction appeal).

As a result, of the large number of reversals the Federal Circuit hands down, many come after a full trial on the merits. And many of those cases require a *new* trial under a new claim construction. Not only must the litigants try the case before appealing, the *de novo* standard of review means a higher likelihood that they will have to try it a second time. *Cf.*, *e.g.*, *AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 375 F.3d 1367, 1374 (Fed. Cir. 2004) (Newman, J., dissenting) (noting that the court was remanding "for the third time on the issue of claim construction").

Given this question's fundamental impact on patent litigation, the Solicitor General previously ad-

vised this Court that "[i]n an appropriate case, this Court's intervention might be warranted to determine the proper standard of appellate review" where claim construction rests on the resolution of factual disputes. U.S. Amicus Br. at 17, *Retractable*, No. 11-1154 (Nov. 28, 2012); *see id.* at 21. The Solicitor General explained that the Federal Circuit's rule is based on a misreading of this Court's decision in *Markman II*. As he noted, "[t]he Federal Circuit's decision in *Cybor* does not identify any reason that [factual findings underlying claim construction] should not be given the deference ordinarily required by [Rule] 52(a)." *Id.* at 20-21. In a subsequent brief in *Lighting Ballast*, the government expressly called for the Federal Circuit to overrule its precedent holding that factual findings must be reviewed *de novo*.[8]

The government, the dissenting Federal Circuit judges, and their fellow critics of current Federal Circuit precedent have a common theme: a "*clear example*"—perhaps the clearest—"of a factual finding is the historical meaning of a claim term to one of ordinary skill in the art at the time of the invention." U.S. Amicus Br. at 15, *Lighting Ballast*, *supra* (emphasis added); *accord, e.g.*, *Cybor*, 138 F.3d at 1464 (Mayer, J., concurring in the judgment). That is precisely the sort of finding that the district court made—and the Federal Circuit upset—in this case.

For that reason, this is the "appropriate case" that the Solicitor General urged this Court to await. The standard-of-review question is squarely presented,

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[8] The government is joined in that position by numerous other amici, including the American Bar Association, the American Intellectual Property Law Association, and the Federal Circuit Bar Association.

and as the Solicitor General recognized, that question meets the standards for certiorari.

II. This Case Is An Ideal Vehicle Allowing This Court To Address This Critical Issue Without Further Delay

A. The District Court's Findings Were Amply Supported And Would Have Been Outcome-Determinative

The last high-profile case raising the standard-of-review question, *Retractable*, unfortunately turned out not to be a proper vehicle, because the district court made no findings and took no expert or documentary evidence. U.S. Amicus Br. at 21-22, *Retractable, supra*. In fact, there was nothing on which to base findings except "the legal arguments of counsel." *Id.* at 18. The standard of review for factual findings therefore did not matter.

In this case, by contrast, that issue is presented cleanly—indeed, quite starkly. The district court found as a factual matter that a person of skill in the art would know what "average molecular weight" meant as used in the patents. Crediting that finding would mean the patents were not hopelessly indefinite—and would reverse the outcome of this case. But three generalist appellate judges refused to credit it, simply because they disagreed with it—for reasons that the district court's findings anticipated, addressed, and refuted. On clear-error review, such disagreement plainly would not have been enough to justify reversal. Respondents prevailed purely because, as the Federal Circuit stated twice, it reviewed the finding "*de novo*." Pet. App. 7a, 10a. That standard of review—and nothing else—allowed

the Federal Circuit to decide for itself that highly trained chemists familiar with peptide synthesis would not have been able to decipher the meaning of this patent.

The district court was quite clear about the difference between factual findings based on expert evidence, which are entitled to deference under Rule 52(a)(6), and legal arguments by lawyers. The court observed that Sandoz relied heavily "on unsubstantiated attorney-argument," which could not outweigh the expert evidence Teva submitted. Pet. App. 49a-50a. For its part, Mylan submitted expert evidence, which was simply less persuasive than Teva's.

Teva's expert, Dr. Grant, repeatedly explained in detail what a "person of skill in the art would [or would not] have understood" by particular terms used in the patents. *Id.* at 92a-93a, 125a-130a. He also explained how a person of skill in the art would have understood the statement in the prosecution history on which the panel relied. *Id.* at 128a-129a.

The district court made findings crediting Dr. Grant's testimony—including, where necessary, over the testimony of Mylan's expert. *See* pp. 11-12, *supra*; Pet. App. 48a-50a, 52a, 55a-57a. In fact, when the court of appeals relied on the fact that the peaks of the curves in Figure 1 did not precisely correspond to the average-molecular-weight figures in Example 1, it was making precisely the same point that Mylan introduced *through its expert*. *See id.* at 10a-11a, 49a. The district court credited Dr. Grant's explanation of that minor discrepancy as a technical artifact. *Id.* at 49a. In reversing, the court of appeals was simply rejecting the district court's factfinding—

without offering *any* reason why Dr. Grant or the district court was clearly wrong.

Respondents have contended that this case presents an unsuitable context in which to consider applying Rule 52(a)(6), because Dr. Grant did not testify in person. For that reason, respondents have argued, the district court's findings based on his testimony are not entitled to deference. Resps.' Opp. to Stay Appl. 12-13 ("The court of appeal was in as good a position as the district court to review [the expert declarations]."). But this Court has squarely rejected that exact argument in the context of Rule 52(a)(6), through both case law and rulemaking. The plain text of the Rule states that the clear-error standard of review applies with full force to all "findings of fact, whether based on oral *or other* evidence." Fed. R. Civ. P. 52(a)(6) (emphasis added). That amendment came about precisely because some courts of appeals concluded that—just as respondents have argued—they were in "as good a position as the trial court to review a purely documentary record," Fed. R. Civ. P 52 advisory committee's note (1985). This Court amended the Federal Rules to disapprove those decisions and make clear that the clear-error standard of review is *not* limited to findings based on oral testimony. *Id.*; *accord Anderson v. City of Bessemer City*, 470 U.S. 564, 574 (1985) ("The rationale for deference to the original finder of fact is not limited to the superiority of the trial judge's position to make determinations of credibility."). In-person credibility determinations are to be paid "special deference," but that "does not alter" the Rule's basic command: when a district court makes a factual finding, it is reviewed for clear error, no matter the

kind of case. *Id.* (citing *Pullman-Standard*, 456 U.S. at 287.

Thus, there is no need for this Court to wait and decide the question presented in the context of some future case involving oral testimony. Indeed, the case the Federal Circuit is now considering en banc, *Lighting Ballast*, also involves an expert declaration—a much less detailed submission than Dr. Grant's.[9] Rule 52(a)(6) does not permit a rule that defers to oral testimony but allows *de novo* review of documentary evidence. There is therefore no reason to wait for a case involving oral testimony to decide the basic question of *de novo* versus clear-error review.

B. This Court Should Not Delay Review Any Longer

This Court might well have taken up this question two Terms ago if the *Retractable* case had proved to be a suitable vehicle. *See* U.S. Amicus Br. at 21, *Retractable*, *supra*. Respondents cannot dispute that the question continues to be crucially important to numerous facets of patent litigation. And the holding of *Cybor* is no more correct today than it was in 2012.

Rather than dispute the importance of the question presented, respondents have contended that the final

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[9] *See* En Banc Br. of Deft.-Appellant at 55-56, *Lighting Ballast*, No. 2012-1014 (Fed. Cir. May 20, 2013) ("[T]he district court did not hold a claim construction hearing or evaluate the live testimony of any witnesses. The record consisted of the patent, the prosecution history, [an expert]'s nine page-long declaration, and a few excerpts from [an inventor]'s deposition transcript.") (citations omitted).

answer should come from the Federal Circuit, in *Lighting Ballast*, rather than this Court. *See, e.g.*, Resps.' Opp. to Stay Appl. 10-11. Respondents have characterized the question as implicating only an "internal division" or "'internal difficulties'" within the Federal Circuit. *Id.* (quoting *Wisniewski v. United States*, 353 U.S. 901, 902 (1957)). So, they contend, the Federal Circuit's decision to rehear *Lighting Ballast* en banc signals that a definitive resolution to the matter is at hand, and this Court should not step in. That argument carries no weight.[10] Quite simply, a decision by today's Federal Circuit judges, no matter what it may be, cannot provide a sure and certain answer to this question. Only this Court can do that, not only because the question is so important, but because the answer depends on resolving what *this Court* has said.

That is why none of the Federal Circuit's previous decisions has settled this issue. To the contrary, the continued discord within the Federal Circuit has *increased* the uncertainty that surrounds this foundational issue of patent litigation. The Federal Circuit has considered the issue en banc three different times since 1995, and a fourth is now underway. *See Markman I*, 52 F.3d at 976-77, 979; *Cybor*, 138 F.3d at 1454-56; *Phillips*, 415 F.3d at 1328; *Lighting Ballast, supra*. Each time thus far, it has attracted great attention and a flood of briefing from interested *amici* on all sides. Each time thus far, it has ul-

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[10] Under analogous circumstances, this Court has granted review of an important question when a suitable vehicle presented itself, even though the sole outlier court of appeals had already granted rehearing en banc whether to overrule its precedent and eliminate the circuit split. *See, e.g., Dillon v. United States*, 130 S. Ct. 2683, 2693 n.6 (2010).

timately left the law where it stands today. *See generally* pp. 4-7, *supra*.

Yet each time, the dissenters have vowed to keep up the fight. *See, e.g.*, *Phillips*, 415 F.3d at 1330, 1334 (Mayer, J., dissenting) ("Now more than ever I am convinced of the futility, indeed the absurdity, of this court's persistence in adhering to the falsehood that claim construction is a matter of law devoid of any factual component. We should abandon this unsound course."). New judges have joined them. *See, e.g.*, *Retractable*, 659 F.3d at 1373 (O'Malley, J., dissenting from denial of rehearing en banc); *id.* (Moore, J., dissenting from denial of rehearing en banc). And other judges have expressed uncertainty about the merits but agreed that the question should be reconsidered. *See, e.g.*, *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1040 (Fed. Cir. 2006) (Michel, C.J., dissenting from denial of rehearing en banc) ("[I]n light of our eight years of experience with [the] application" of the *Cybor* rule of *de novo* review, "I have come to believe that reconsideration is appropriate and revision may be advisable."); *id.* at 1045 (Gajarsa, Linn, and Dyk, JJ., concurring in denial of rehearing en banc) ("In an appropriate case we would be willing to reconsider limited aspects of the *Cybor* decision.").

In short, this debate has occupied the Federal Circuit for nearly two decades. The holding of *Lighting Ballast*—whichever way the case comes out—will not suddenly provide the certainty that patent litigants and lawyers have been seeking. Compounding the problem, the Federal Circuit voted to grant rehearing in *Lighting Ballast* at a time when three of its twelve judgeships were vacant. All three seats have

now been filled, but only one of them in time for the new judge to hear argument in *Lighting Ballast*. A majority of the en banc court thus might not represent a majority of the sitting judges—which would only encourage further attempts to relitigate the issue.

Continued litigation is a certainty because those favoring *de novo* review of factual findings insist, and will continue to insist, that this Court has already settled the matter. The Federal Circuit majority has pointed to this Court's holdings that claim construction *in general* is a matter of law;[11] to the Court's decision that factual issues underlying claim construction are resolved by the judge;[12] to the Court's endorsement of the general proposition that uniform interpretation of patents is a good thing;[13] and even to the Court's failure to mention the standard of appellate review in *Markman II*.[14]

As explained above, and as many litigants, *amici* (including the Government), and commentators have discussed, those views are incorrect. But more significantly, they also demonstrate the enduring na-

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[11] *Markman I*, 52 F.3d at 981 (citing numerous hoary patent cases).

[12] *Cybor*, 52 F.3d at 1456-57 ("[T]he Supreme Court' s opinion [in *Markman II*] conclusively and repeatedly states that claim construction is purely legal.").

[13] *Id.* at 1455 (in *Markman II*, "the Supreme Court endorsed [the Federal Circuit's] role in providing national uniformity to the construction of a patent claim, a role that would be impeded if we were bound to give difference to a trial judge's asserted factual determinations incident to claim construction.").

[14] *Id.* ("Nothing in the Supreme Court's opinion supports the view that the Court endorsed a silent, third option—that claim construction may involve subsidiary or underlying questions of fact.").

ture of the problem. Until this Court takes up this question and answers it, the controversy within the Federal Circuit is likely to continue, and patent litigation will continue to be plagued with uncertainty.

Because *Lighting Ballast* will not settle the issue, this Court need not and should not wait for a future petition in *Lighting Ballast*. Recent experience has shown that the Court cannot count on the litigants in a patent case, even a high-profile, precedent-setting patent case, to seek review.[15] And if this Court were to wait, the Federal Circuit would continue to apply its misguided rule of *de novo* review in case after case while *Lighting Ballast* is pending, dozens of them each month. In many of those cases, including this one, the standard of review results in a new claim construction that either changes the winner or requires a new trial.

Rather than defer taking up an issue that it *will* need to review in an appropriate case, this Court should ask at the certiorari stage whether this case properly presents the eminently cert-worthy issue. The answer is yes. The Court should not pass up this opportunity to take a case in which the issue is so plainly outcome-determinative and in which the court of appeals' disregard of the factual findings about the state of knowledge in the art was so complete.

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[15] In several recent Federal Circuit en banc cases, the losing party has not petitioned for certiorari. *See, e.g., Marine Polymer Techs., Inc. v. HemCon, Inc.*, 672 F.3d 1350 (Fed. Cir. 2012); *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011); *TiVo, Inc. v. EchoStar Corp.*, 646 F.3d 869 (Fed. Cir. 2011); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010).

C. Because The Court May Have The Opportunity To Address This Question In A Case Already Pending, The Court May Wish To Hold The Petition

The role of factual findings in claim construction is so fundamental that it has surfaced in a case that this Court will hear on the merits this Term. In *Nautilus, Inc. v. Biosig Instruments, Inc.*, No. 13-369, the Court will consider the standard governing the indefiniteness defense in patent-infringement litigation. Both questions presented in *Nautilus* bear on the Federal Circuit's decision in this case, and the second question directly implicates the issue raised in this petition. The possibility that the Court will address that issue this Term would justify holding this petition pending *Nautilus*. But if the Court decides not to answer that question in *Nautilus*, it should grant review in this case without delay.

As noted above, under Federal Circuit precedent, to establish that a patent is indefinite under 35 U.S.C. § 112 ¶ 2, challengers must prove that the claim is not amenable to construction or is "insolubly ambiguous." Pet. App. 6a (quoting the panel opinion in *Nautilus*). The Court has now agreed to review whether the "insolubly ambiguous" standard is correct, and whether the statutory presumption of patent validity (35 U.S.C. § 282 (2006)) "dilutes" the definiteness requirement. Pet. for Cert. at i, *Nautilus*, No. 13-369 (Sept. 21, 2013).

The parties appear likely to argue the presumption-of-validity question in a way highly relevant to this case. Under this Court's decisions, the presumption of validity means that a patent-invalidity defense must be proven by clear and convincing evi-

dence. *See generally Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238 (2011). The patentee in *Nautilus* contended at the certiorari stage that, because indefiniteness involves consideration of *factual issues as part of claim construction*, the presumption requires those facts to be supported by clear and convincing evidence. Br. in Opp. at 31, *Nautilus, supra*. And the patentee emphasized that it submitted expert evidence that a person of ordinary skill in the art could understand what is claimed by the patent. *Id.* at 32. The petitioner responded that the presumption of validity was inapplicable because "[t]here are no factual determinations in claim construction." Cert. Reply Br. at 6, *Nautilus, supra*. And *both* briefs relied on this Court's decision in *Markman II* for those competing propositions—just as the judges of the Federal Circuit have done in expressing their divergent views on the proper standard of appellate review, *see* pp. 4-7, 21-23, *supra*.

As Justice Breyer noted in *i4i*, understanding the proper role of the presumption of validity calls for the Court to "separat[e] factual and legal aspects of an invalidity claim." 131 S. Ct. at 2253 (Breyer, J., joined by Scalia and Alito, JJ., concurring). Accordingly, deciding whether the presumption of validity "dilutes" the statutory requirement of clear claim drafting is likely to turn on the question presented by this petition: whether claim construction turns on underlying questions of fact, subject to review under Rule 52(a)'s "clear error" standard, or is a pure question of law.

The Federal Circuit itself has been inconsistent in its approach to that issue. Decisions like the one below treat the indefiniteness inquiry as a purely legal

question reviewed *de novo*. *See, e.g.*, Pet. App. 7a ("Indefiniteness is a question of law we review de novo.").[16] But other decisions correctly recognize that the ultimate legal conclusion whether a claim is indefinite often depends on underlying factual questions entitled to deferential review. *See, e.g.*, *BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1370-71, 1372-73 (Fed. Cir. 2003) (treating as a matter of fact, reviewed deferentially, whether a person of ordinary skill in the art would know what "about 0.06" includes).[17]

In light of the questions presented in *Nautilus*, the parties' contentions, and the split within the Federal Circuit, the Court may well address the proper role of factual findings in claim construction in the course of deciding *Nautilus*. The Court therefore may wish to hold the petition in this case pending a decision in *Nautilus*.[18] But if this Court does not resolve the

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[16] *Accord, e.g.*, *Funai Elec. Co., Ltd. v. Daewoo Elecs. Corp.*, 616 F.3d 1357, 1371 (Fed. Cir. 2010) ("The issue of claim definiteness receives plenary review, as a question of law."); *Atmel Corp. v. Info. Storage Sys.*, 198 F.3d 1374, 1378 (Fed. Cir. 1999) (reviewing *de novo*).

[17] *Accord Southwest Software, Inc. v. Harlequin Inc.*, 226 F.3d 1280, 1288, 1297-98 (Fed. Cir. 2000) (treating indefiniteness as a question of fact rather than law).

[18] This case may also be informed by the Court's disposition of *Highmark Inc. v. Allcare Health Mgmt. Sys.*, No. 12-1163, and *Octane Fitness, LLC v. Icon Health & Fitness, Inc.*, No. 12-1184 (both to be argued Feb. 26, 2014). The Court is considering whether the Federal Circuit has erroneously asserted authority to review *de novo* a district court's finding that a patent case is an exceptional one warranting an award of attorney's fees. The parties, and dissenting judges in the Federal Circuit, have emphasized that the Federal Circuit's position in *Highmark* bears considerable similarity to its position on claim construction in *Cybor*: it has assumed the power to review *de novo* by labeling

standard-of-review issue in the course of deciding *Nautilus*, this case represents the Court's best opportunity to settle the question definitively, without further delay.

* * * * *

For too long, the Federal Circuit has seized for itself the primary role in claim construction, even on complex, technical factual points. The district court is in a far better position to invest the time and attention necessary to understand the patent from the right perspective—that of a person skilled in the art. That is exactly what the district court did in this case. Teva's expert gave, and the district court credited, several reasons why "average molecular weight" was not fatally ambiguous to a skilled artisan. The Federal Circuit panel disagreed—without even acknowledging that the question is supposed to be examined from a skilled artisan's perspective. The panel's decision to second-guess the district court's well-informed findings and hold the patent hopelessly ambiguous well illustrates the problem with the *Cybor* rule. This Court should take this clear, concrete, and ready opportunity to examine that rule—and to reject it.

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an entire issue a "legal" one, even when it turns on fact questions. *E.g.*, Pet'r Br. at 17, *Highmark*, No. 12-1163); *Highmark, Inc. v. Allcare Health Mgmt. Sys., Inc.*, 701 F.3d 1351, 1362 (Fed. Cir. 2012) (Moore, J., dissenting from denial of rehearing en banc); *Highmark, Inc. v. Allcare Health Mgmt. Sys., Inc.*, 687 F.3d 1300, 1320 (Fed. Cir. 2012) (Mayer, J., dissenting in part). To the extent not subsumed in a hold for *Nautilus*, a hold for *Highmark* and *Octane* would also be appropriate.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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January 16, 2014

APPENDIX

APPENDIX A

United States Court of Appeals for the Federal Circuit

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA NEUROSCIENCE, INC., AND YEDA RESEARCH AND DEVELOPMENT CO., LTD.,
Plaintiffs-Appellants,

v.

SANDOZ, INC., AND MOMENTA PHARMACEUTICALS INC.,
Defendants-Appellants,

AND

MYLAN PHARMACEUTICALS INC., MYLAN INC., AND NATCO PHARMA LTD.,
Defendants-Appellants,

AND

SANDOZ INTERNATIONAL GMBH, AND NOVARTIS AG,
Defendants.

2012-1567, -1568, -1569, -1570

Appeals from the United States District Court for the Southern District of New York in consolidated

Nos. 08-CV-7611 and 09-CV-8824, Judge Barbara S. Jones.

Decided: July 26, 2013

ELIZABETH J. HOLLAND, Kenyon & Kenyon, LLP, of New York, New York, argued for plaintiffs-appellees. Of counsel on the brief were WILLIAM G. JAMES, II, of Washington, DC; DAVID M. HASHMALL, Goodwin Procter, LLP, of New York, New York; JOHN C. ENGLANDER, HENRY C. DINGER, DARYL L. WIESEN, JOHN T. BENNETT, and NICHOLAS K. MITROKOSTAS, of Boston, Massachusetts.

DEANNE E. MAYNARD, Morrison & Foerster, LLP, of Washington, DC, argued for defendants-appellants, Sandoz Inc., et al. With her on the brief were BRIAN R. MATSUI, and MARC A. HEARRON; DAVID C. DOYLE, ANDERS T. AANNESTAD and BRIAN M. KRAMER, of San Diego, California.

EVAN R. CHESLER, Cravath Swaine & Moore LLP, of New York, New York, argued for defendants-apellants, Mylan Pharmaceuticals, Inc., et al. on the brief were SHANNON M. BLOODWORTH and BRANDON M. WHITE, Perkins Coie, LLP, of Washington, DC; and DAVID L. ANSTAETT and DAVID E. JONES, of Madison, Wisconsin. Of counsel was JOHN SINGLETON SKILTON, Perkins Coie, LLP, of Madison, Wisconsin.

Before RADER, *Chief Judge*, MOORE, *Circuit Judge*, and BENSON, *District Judge*.*

MOORE, *Circuit Judge*.

The defendants in these consolidated patent infringement actions (collectively, Appellants) appeal from the district court's judgment that various claims of the nine patents-in-suit asserted by the plaintiffs (collectively, Teva) are infringed, and from the court's holdings regarding indefiniteness, nonenablement, and obviousness.[1] We hold that Group i claims are invalid for indefiniteness, but that Group ii claims have not been proven indefinite.[2] We also hold that the district court did not err in its conclusions that the claims are infringed, and that the Appellants failed to prove that the claims would have been obvious and are not enabled. Accordingly, we *affirm* the district court's judgments of infringement and no invalidity with respect to Group ii claims, *reverse* its judgment of no invalidity with respect to Group I claims, and *remand*.

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* Honorable Dee V. Benson, District Judge, United States District Court for the District of Utah, sitting by designation.

[1] The asserted patents are: U.S. Patent Nos. 5,800,808 ('808 patent), 5,981,589 ('589 patent), 6,048,898 ('898 patent), 6,054,430 ('430 patent), 6,342,476 ('476 patent), 6,362,161 ('161 patent), 6,620,847 ('847 patent), 6,939,539 ('539 patent), and 7,199,098 ('098 patent).

[2] The six Group II claims are: claims 1 and 2 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, and claims 1 and 8 of the '098 patent. The remaining claims are collectively referred to as Group I claims.

BACKGROUND

Appellants submitted Abbreviated New Drug Applications (ANDAs) to the Food and Drug Administration (FDA) seeking approval to market generic versions of Copaxone®, a drug used in treating multiple sclerosis. Two proposed generic products, the Mylan accused product and the Sandoz accused product, are at issue in this appeal. Teva, which markets Copaxone®, sued Appellants for patent infringement under 35 U.S.C. § 271(e)(2)(A). The patents-in-suit, which share a common specification, are listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) entry for Copaxone®. The patents-in-suit include claims reciting a product called copolymer-1 and claims reciting methods of making copolymer-1.

Copolymer-1 consists of four different amino acids (al-anine, glutamic acid, lysine, and tyrosine) combined in a certain ratio to make a polypeptide product. A sample of polymeric material like copolymer-1 typically consists of a mixture of individual polymer molecules that have varying molecular weights. There are different ways to describe the resulting distribution of molecular weight values. One approach uses statistical measures, including the peak average molecular weight (M_p), number average molecular weight (M_n), and weight average molecular weight (M_w). M_p is the molecular weight of the most abundant molecule in the sample. M_n is the arithmetic mean, or the total mass of all the molecules in the sample divided by the total number of molecules. M_w is still another

average molecular weight measure that is calculated differently from M_p and M_n. In a typical polymer sample, M_p, M_n, and M_w have different values.

A second approach describes how many molecules in a polymer sample have molecular weights that fall within an arbitrarily set range. For example, if 99% of the constituent molecules in a sample have molecular weights between 1 kilodalton (kDa) and 100 kDa, the sample may be described as having 99% of its mole fraction within the molecular weight range of 1 kDa to 100 kDa.

The claims of the patents-in-suit use both approaches. Claim 1 of the '589 patent is representative of Group I claims, which use the first approach:

> Copolymer-1 having *a molecular weight of about 5 to 9 kilodaltons*, made by a process comprising the steps of:
>
> reacting protected copolymer-1 ; and
>
> purifying said copolymer-1, to result in copolymer-1 *having a molecular weight of about 5 to 9 kilo-daltons*.

'589 patent claim 1 (emphases added). Claim 1 of the '430 patent is representative of Group II claims, which use the second approach: "Copolymer-1 having over *75% of its mole fraction within the molecular weight range from about 2 kDa to about 20 kDa* " '430 patent claim 1 (emphasis added).

In its claim construction order, the district court did not distinguish in detail between the different

contexts in which the term "molecular weight" is used in Group I and Group II claims. The court rejected the Appellants' argument that the term "molecular weight" was insolubly ambiguous because it could refer to M_p, M_n, M_w, or yet another average molecular weight measure. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 810 F. Supp. 2d 578, 586-93, 596 (S.D.N.Y. 2011) (*Markman Order*). It construed "molecular weight" as M_p and held that the claims are not indefinite. *Id.* After a bench trial, the court held that the asserted claims are not invalid for obviousness or lack of enablement, and that the Mylan and Sandoz accused products infringe all of the asserted claims. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295 (S.D.N.Y. 2012) (*Opinion*).

This appeal followed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

I. Definiteness

A patent's specification "must conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor regards as the invention." 35 U.S.C. § 112(b) (2012). "A claim is indefinite only when it is not amenable to construction or insolubly ambiguous." *Biosig Instruments, Inc. v. Nautilus, Inc.*, 715 F.3d 891, 898 (Fed. Cir. 2013). To prove indefiniteness, "an accused infringer must demonstrate by clear and convincing evidence that one skilled in the relevant art could not discern the boundaries of the claim based on the claim language, the specification, the prosecution

history, and the knowledge in the relevant art." *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1366 (Fed. Cir. 2011). Indefiniteness is a question of law that we review *de novo*. *Id.* at 1365-66.

Appellants argue that the term "molecular weight" renders all of the asserted claims indefinite because it can refer to different measures, including M_p, M_w, and M_n. They contend that the scope of the claims varies significantly depending on the measure and that a skilled artisan cannot ascertain the boundaries of the claims. Appellants argue that Teva inconsistently defined "molecular weight" as M_w and M_p during prosecution of two of the familial patents, reinforcing the ambiguity. Further, Appellants contend that the specification does not resolve which molecular weight measure is intended.

Appellants also contend that their indefiniteness arguments apply equally to Group I and Group II claims. They argue that even Group II claims, which refer to a molecular weight range, "necessarily refer to a copolymer-1 percentage above or below a certain average molecular weight." Sandoz Reply Br. 17. Appellants contend that, because all of the claims recite "molecular weight," they must be indefinite.

Teva counters that the prosecution history clarifies that "molecular weight" should be construed as M_p. It contends that its response to an indefiniteness rejection of the '539 patent claims unequivocally stated that a person of skill in the art reading the specification would understand that the term "molecular weight" refers to M_p. Teva argues that the district court correctly determined that its response during prosecution of the '847 patent, where it stated

that "[o]ne of ordinary skill in the art could understand that kilodalton units implies [sic] a weight average molecular weight," was not contradictory. J.A. 3229. It contends that a skilled artisan would discount this statement because it does not explicitly define "molecular weight" as M_w and because it contains an evident scientific error—any molecular weight measurement, not just Mw, may be expressed in kilodalton units.

Teva also contends that the specification resolves any ambiguity in the meaning of "molecular weight." Teva contends that the specification's reference to the Size Exclusion Chromatography (SEC) method indicates that "molecular weight" means M_p because determining M_n and M_w requires further calculations from SEC data that the specification does not describe. It further argues that Figure 1 confirms this conclusion because only M_p can be obtained directly from the molecular weight plot in that figure.

Finally, Teva contends that Group II claims refer to exact molecular weight values and are therefore not ambiguous. It argues that Group II claims recite percentages of molecules in a copolymer-1 sample that fall within a specified molecular weight range, not average values.

We agree with Appellants that Group I claims are indefinite and agree with Teva that Group II claims are not. It is undisputed that Group I claims contain an ambiguity because their plain language does not indicate which average molecular weight measure is intended. Teva's attempt to resolve this ambiguity hinges in part on the prosecution history. But two of

its prosecution statements directly contradict each other and render the ambiguity insoluble.

During prosecution of the '539 patent, the Examiner rejected pending claims as indefinite, stating that "the term 'average molecular weight' is indefinite since its method of measurement is not specified, i.e. [M_n], [M_w] etc." J.A. 3245. Teva stated in its response that "[o]ne of ordinary skill in the art, upon reviewing the specification, would understand that 'average molecular weight' refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1," *i.e.*, M_p. J.A. 3258. The claims were allowed. During prosecution of the '847 patent, the Examiner made an analogous rejection over the same claim term, stating that "the term 'average' molecular weight is meaningless as a limitation without specifying its basis, e.g., [M_w], [M_n], etc." J.A. 3220. Teva overcame the rejection by responding that "[o]ne of ordinary skill in the art could understand that kilodalton units implies [sic] a weight average molecular weight," *i.e.*, M_w. J.A. 3229. The only basis upon which the Examiner could have agreed that the '539 patent claims were not indefinite was that "molecular weight" means M_p. In contrast, the only basis for the Examiner's withdrawal of the indefiniteness rejection of the '847 patent claims was that the same term means M_w. Teva's two definitions cannot be reconciled.

The specification does not resolve the ambiguity. Teva's expert, Dr. Gregory Grant, testified that after examining the curve depicted in Figure 1 and the accompanying legend, a skilled artisan would know

that the claim terms "molecular weight" and "average molecular weight" denote M_p. Dr. Grant also testified that Example 1's discussion of gel filtration, which refers to the SEC method for measuring molecular weight, tells a skilled artisan that "molecular weight" refers to M_p. *See* '808 patent, col. 3 ll. 6-8. He explained that only M_p, which is simply the highest point of a molecular weight curve, can be read directly from a plot of SEC data.

On *de novo* review of the district court's indefiniteness holding, we conclude that Dr. Grant's testimony does not save Group I claims from indefiniteness. As Dr. Grant himself opined, SEC does not exclusively provide M_p— both M_n and M_w can also be obtained from the data generated by the SEC method after some calculations. J.A. 1005. His testimony is consistent with that of one of Appellants' experts, who opined that SEC "can give at least peak average, number average, and weight average 'molecular weights.'" J.A. 1229. Furthermore, as illustrated in the figure below, the peaks of the curves in Figure 1 do not correspond to the values denoted as "average molecular weight" in the figure's legend (Appellants' additions in color). In fact, the 7.7 kDa value is closer to the M_w than to the M_p of the corresponding batch, which makes it difficult to conclude that M_p is the intended measure. J.A. 5285. Thus, we hold that Group I claims are indefinite.

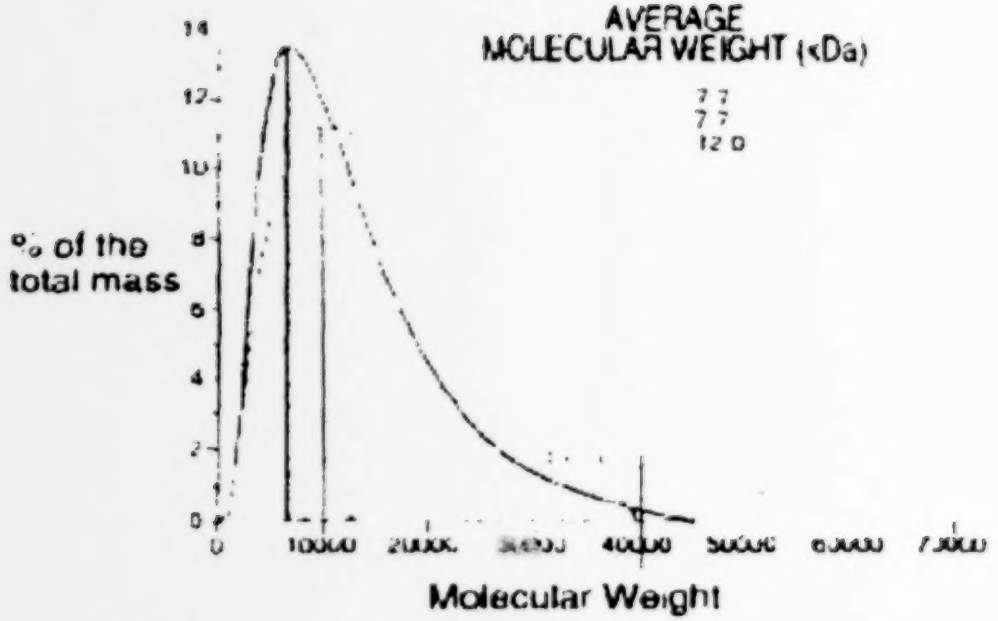

FIG. 1

Group II claims, by contrast, do not recite average molecular weight values. Instead of describing copolymer-1 in terms of a statistical measure, such as M_w, Group II claims recite the percentage of copolymer-1 molecules in a sample falling within an arbitrarily set molecular weight range. The numbers that set the boundaries of that range, such as "2 kDa" and "20 kDa" in the '430 patent claim 1, refer to precise points on the "Molecular Weight" axis, rather than to statistical properties of the polymer molecular weight curves. Like the numbers 10,000 (*i.e.*, 10 kDa) and 20,000 (i.e., 20 kDa) in the figure above, "2 kDa" and "20 kDa" refer to exact values rather than statistical measures. The scope of Group II claims is thus readily ascertainable. We hold that Group II claims are not invalid for indefiniteness.

II. Enablement

A patent's specification must describe the invention and "the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains to make and use the same." 35 U.S.C. § 112(a). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012) (internal quotation marks omitted). Enablement is a question of law that we review without deference, based on underlying factual inquiries that we review for clear error after a bench trial. *Cephalon, Inc. v. Watson Pharm, Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013).

The district court held that Appellants failed to prove that the asserted claims are not enabled for making copolymer-1 at the claimed molecular weight because a person of skill in the art would be able to measure it using either of two known calibration methods, "self-standards" or "universal calibration." *See Opinion*, 876 F. Supp. 2d at 382-99. The court determined that polymer literature at the time of filing described both methods in detail, and that those methods could be adapted to copolymer-1. The court also found that Teva's own extensive post-filing experimentation with measurement methods did not conclusively establish lack of enablement. The court thus rejected Appellants' experts' testimony that undue experimentation would be required, holding instead that the specification and background

knowledge in the art provided sufficient guidance on measuring the molecular weight.

Appellants argue that the district court erred in its enablement analysis. They contend that the specification states only that the SEC column should be "calibrated" and does not disclose which calibration standards should be used to measure the molecular weight. '808 patent, col. 3 ll. 6-8. Appellants argue that general SEC calibration methods do not readily apply because copolymer-1 is complex and exhibits unpredictable behavior. They further point to expert testimony that the commercially available standards that a skilled artisan would have been most likely to pick are in fact unreliable for measuring the molecular weight of copolymer-1.

Appellants also argue that the evidence of Teva's own difficulties with identifying appropriate calibration methods, which they contend the district court disregarded, confirms that the claims are not enabled. Appellants contend that Teva's various internal documents show the allegedly challenging development of calibration standards for measuring the molecular weight of copolymer-1, and point out that Teva deleted references to the standards from the patent application before filing. They argue that Teva's problems with molecular weight measurements continued after filing, noting that Teva switched calibration standards during the FDA approval process. Appellants thus contend that the asserted claims are not enabled because the specification does not teach which standards a

skilled artisan must use to calibrate copoly-mer-1 molecular weight measurements.

We perceive no clear error in the fact findings on which the district court based its enablement conclusion. Dr. Grant testified at length that it would have been routine for a skilled artisan to measure the molecular weight of copolymer-1. *See, e.g.*, J.A. 19671, 20474, 20752-54. He explained that, by calibrating the SEC column mentioned in the specification using methods that were well known at the time of filing, a skilled artisan could confirm the synthesis of copolymer-1 within the claimed molecular weight range. *Id.* The district court weighed this testimony against that of Appellants' experts and found it to be more convincing. *See, e.g.*, *Opinion*, 876 F. Supp. 2d at 398 (Appellants' expert "failed to address the extensive literature that existed [at the time of filing] regarding SEC, self-standards, and universal calibration."); *see also id.* at 392. We thus agree with Teva that the district court did not err in concluding that utilizing the calibration methods discussed by Dr. Grant would not require undue experimentation.

Appellants' arguments relating to Teva's own alleged calibration struggles also fail to demonstrate that the district court committed a reversible error. Appellants' assertion that the district court ignored Teva's internal experimentation is simply inaccurate. *See id.* at 391. Moreover, Appellants point to no evidence that undermines the district court's understanding that "it is entirely plausible that Teva experimented with different methods to deal with regulatory and other scale-up issues, rather than to

correct faulty measurements." *Id.*; *see also Edwards Lifesciences AG v. CoreValve, Inc.*, 699 F.3d 1305, 1309-10 (Fed. Cir. 2012) (explaining that failure to enable a commercial embodiment does not demonstrate nonenablement under 35 U.S.C. § 112(a)). Nor do Appellants adequately explain why the claimed invention cannot be practiced without the calibration method that Teva deleted from its draft patent application. We therefore affirm the district court's conclusion of no invalidity for lack of enablement.

III. Obviousness

A patent claim is invalid under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." "Obviousness is a legal conclusion based on underlying facts." *Allergan, Inc. v. Sandoz Inc.*, _ F.3d _, 2013 WL 1810852, at *4 (Fed. Cir. May 1, 2013). "The underlying factual considerations in an obviousness analysis include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations," which include "commercial success, long-left but unsolved needs, failure of others, and unexpected results." *Id.* (citations omitted).

The district court held that the asserted claims would not have been obvious in view of copolymer-1 compounds with a molecular weight higher than 10

kDa disclosed in U.S. Patent No. 3,849,550 (Teitelbaum) and other prior art references. *Opinion*, 876 F. Supp. 2d at 401-19. It found that Teitelbaum disclosed a preference for copoly-mer-1 compositions having molecular weights of 18-20 kDa and greater, and that other references explicitly taught away from the claimed lower molecular weight copolymer-1. The court also determined that various secondary considerations supported the conclusion of nonobviousness.

Appellants argue that the asserted claims would have been obvious because the claimed copolymer-1 differs from known copolymer-1 by only one kilodalton unit and behaves similarly to the prior art material. Specifically, they contend that there is no evidence that copolymer-1 with a molecular weight less than 10 kDa exhibits an improved toxicity profile over the prior art copolymer-1. Appellants also dispute the district court's conclusion that the prior art taught away from the claimed invention. They acknowledge that one paragraph in a 1974 prior art reference stated that copolymer-1 with a molecular weight lower than 17 kDa was ineffective for treating multiple sclerosis. *See* J.A. 49058-59. But they counter that more recent art taught that copolymer-1 of lower molecular weight yielded promising results in human trials. *See* J.A. 36696-702. With regard to secondary considerations, Appellants urge that Teva failed to prove a nexus between lower molecular weight and Copaxone®'s commercial success. They further contend that there was no long-felt need for the claimed material because higher molecular weight copolymer-1 was known to be effective.

We see no error in the district court's obviousness analysis. The court did not clearly err when it found that the prior art expressed a preference for higher molecular weight copolymer-1, and therefore taught away from the claimed invention. *See, e.g.*, Teitelbaum, col. 1 ll. 61-62, col. 2 ll. 19-32; *see also* J.A. 20391-93, 49058-59. The court also did not clearly err in the fact findings relevant to secondary considerations, which further support the conclusion of nonobviousness. For example, the court found that "Copaxone® is coextensive with the asserted claims," *Opinion*, 876 F Supp. 2d at 406, triggering a presumption of a nexus between the drug's commercial success and the claimed invention, *see Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). Because Copaxone®'s commercial success is undisputed and Appellants have not rebutted the presumption of a nexus, this consideration favors Teva. We affirm the district court's determination that Appellants failed to establish that the claimed invention would have been obvious.

IV. Infringement

Claim construction is an issue of law that we review *de novo*. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454-55 (Fed. Cir. 1998) (en banc). In construing a claim term, we look at the term's plain meaning. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). "There are only two exceptions to this general rule: 1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of a claim term either in the specification

or during prosecution." *Thorner v. Sony Computer Entm't Am., LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). In order for the doctrine of prosecution disclaimer to apply, a statement in prosecution must constitute a clear and unmistakable disclaimer of claim scope. *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1326 (Fed. Cir. 2003). Infringement is a question of fact reviewed for clear error after a bench trial. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).

The district court construed "copolymer-1" to mean "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1." *Markman Order*, 810 F Supp. 2d at 585; see '808 patent, col. 1 ll. 32-43. This construction is not in dispute. The court explained after trial that, in order to facilitate a comparison with the accused products, it converted the 6:2:5:1 ratio into percentages (42.9% alanine, 14.3% glutamic acid, 35.7% lysine, and 7.1% tyro-sine). *Opinion*, 876 F. Supp. 2d at 336, 339-40. Based on various examples of copolymer-1 disclosed in the references cited in the specification, the court determined that an accused product meets the "approximately 6:2:5:1" limitation as long as its amino acid composition does not vary from the "ideal" percentages by an aggregate of more than 12%. *Id.* at 340. The court found that the Mylan accused product and the Sandoz accused product differ from the "ideal" percentages by an aggregate of 4.4% and 4.5% respectively, and thus infringe literally. *Id.* at 335-44, 356-63. The court also found that Mylan and Sandoz infringe under the doctrine of equivalents because the overall differences

between the amino acid amounts in the claims and the accused products are insubstantial. *Id.* at 345-49, 358.

A. Standard of Review

The parties dispute whether the district court's consideration of the percentages in conjunction with its consideration of the "approximately 6:2:5:1" limitation constitutes a "derivative" claim construction or a part of its infringement analysis. The former is a question of law; the latter is a question of fact. We hold that whether the amino acid percentages in the accused products meet the "approximately 6:2:5:1" limitation is a part of the district court's infringement analysis. Thus, we review the district court's conclusions for clear error.

B. "Approximately 6:2:5:1"

Appellants argue that the district court erred in its analysis of "approximately 6:2:5:1." They contend that the 6:2:5:1 ratio captures *relative* proportions of the four amino acids in copolymer-1 to one another. Appellants argue that the court "eviscerated" these relationships by analyzing "approximately 6:2:5:1" in terms of an *aggregate* amount of percent variation in the amino acid content. Mylan Br. 30. Appellants urge that examples of copolymer-1 in the references cited in the specification define the scope of "approximately 6:2:5:1," and argue that these examples allow for at most 16% variation of any particular amino acid from the "ideal" 6:2:5:1 ratio.

Appellants point out that their products contain the four amino acids in the ratios 4.6: 1.6: 3.7: 1.0

(Mylan product) and 4.6: 1.5: 3.7: 1.0 (Sandoz product). They argue that the accused products do not literally infringe the asserted claims because, for example, the ratio of lysine to tyrosine, 3.7: 1, deviates by more than 16% from the "ideal" ratio of 5:1. Appellants further contend that the district court erred in its finding of infringement under the doctrine of equivalents because its analysis vitiated the "6:2:5:1" requirement.

Teva counters that the district court rightly decided, based on the intrinsic record and expert testimony, that "approximately 6:2:5:1" covers compositions that differ from the "ideal" percentages by an aggregate of at most 12%. Teva argues that Appellants improperly seek to limit the scope of the claims to prior art examples of copolymer-1. It also contends that Appellants fail to adequately explain why the district court's analysis should have focused on the relative ratios of the four amino acids to one another rather than their proportions relative to the whole.

Teva further contends that Appellants perform a "mathematical sleight of hand" by normalizing the ratio relative to tyrosine, the least abundant amino acid in copolymer-1. Teva Br. 32. Teva points out that, while the 6:2:5:1 ratio sets the scale at 14 (= 6 + 2 + 5 +1), Appellant Mylan's expression of the ratio in its product bases the scale on the incommensurate value of 10.9 (= 4.6 +1.5 + 3.7 + 1.0).[3] Teva argues that, in order to properly compare the Mylan accused product to the claims, the correct way to express the

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[3] These arguments apply equally to Sandoz's accused product.

accused amino acid ratio is 6.0: 2.0: 4.7: 1.3 (i.e., a total of 14) or to perform the comparison in terms of percentages. Teva contends that either of these approaches demonstrates that the accused products meet the "copolymer-1" limitation as construed by the district court. Teva further argues that, when rounding error is taken into account, it becomes clear that the accused products contain the four amino acids in the 6:2:5:1 ratio. Finally, it contends that the district court correctly determined that Appellants infringe under the doctrine of equivalents because the differences between the claims and the accused products are insubstantial.

We agree with Teva that the district court did not clearly err in concluding that the accused products literally infringe the asserted claims. We see no basis for overturning the district court's finding that the 6:2:5:1 ratio must be converted to percentages to ensure a comparison on the same scale with the amino acid percentages in the accused products. That comparison reveals that, in the aggregate, the four percentages in Mylan's product (42.7%, 14.4%, 33.6%, and 9.2%) differ from the "ideal" percentages (42.9%, 14.3%, 35.7%, and 7.1%) by only 4.5%.[4] Furthermore, no single amino acid differs from its corresponding "ideal" percentage by more than about 2%. *Id.* at 338.

The district court did not clearly err in determining that these small differences from the "ideal" percentages mean that the accused products literally

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[4] In Sandoz's product, the corresponding percentages are 43.6%, 14.7%, 33.4%, 8.3%, amounting to an aggregate difference of 4.5% from the "ideal" percentages.

infringe. The court's conclusion is supported by its findings regarding prior art examples of copolymer-1. *See id.* at 339-40. These examples show that, even when one of the amino acids (lysine) differs from its "ideal" percentage by more than 5%, the material is still considered "copolymer-1." *Id.* (discussing "Batch 2"); J.A. 49042. The district court's conclusion is reinforced by the undisputed testimony of Teva's expert, Dr. George Gokel, that the amino acid content in copolymer-1 is uncertain due to experimental variations and measurement errors. *Id.* at 339; J.A. 19825-28. We need not decide whether a material that differs by 12% from the 6:2:5:1 ratio (expressed in percentages) infringes the asserted claims because the Mylan and Sandoz accused products deviate from the ratio by less than 5%. We see no clear error in the district court's determination that these products, which differ from the "ideal" percentages by less than 5% in the aggregate, meet the "approximately 6:2:5:1" limitation. Given this conclusion, we do not need to reach the parties' arguments regarding infringement under the doctrine of equivalents.

3. Prosecution Disclaimer

The district court also rejected Appellants' argument that Teva disclaimed copolymer-1 compositions having M_w greater than 10 kDa during prosecution. *Markman Order*, 810 F. Supp. 2d at 596-98. Appellants challenge this conclusion on appeal. They contend that their proposed products have M_w less than 10 kDa and thus do not infringe.

During prosecution of several of the asserted patents, Teva overcame rejections based on the

Teitelbaum patent by arguing that, in contrast to Teitelbaum's copolymer-1 with a "minimum molecular weight of 10 kilodaltons," the pending claims cover "copolymer-1 having a molecular weight of about 5 to 9 kilodaltons." *E.g.*, J.A. 34747. Teitelbaum does not explain whether its references to "molecular weight" mean M_p or M_w, but cites an article that describes the measurement process in more detail. Teitelbaum, col. 4 ll. 31-32 (citing J.A. 49043).

Appellants argue that Teva's statements constitute a disclaimer of copolymer-1 compositions with Mw greater than 10 kDa. They contend that the article cited in Teitelbaum describes a technique that can measure only M_w. Appellants argue that an ordinary artisan would thus understand the prosecution history statements to refer to M_w and to surrender coverage of any copolymer-1 with M_w greater than 10 kDa.

We agree with Teva that its prosecution history statements do not constitute a clear and unmistakable disclaimer. The phrase "molecular weight of 10 kilodaltons" does not expressly refer to any specific molecular weight measurement—indeed, Group I claims are indefinite due in part to the ambiguity in the meaning of "molecular weight." The connection between this statement and the article cited in Teitelbaum is too attenuated to limit the scope of the claims to copolymer-1 with Mw less than 10 kDa. Moreover, the technique discussed in that article can yield Mw or a different type of molecular weight measure, which fails to resolve the ambiguity.

CONCLUSION

We have considered the parties' remaining arguments and do not find them to be persuasive. We hold that the district court did not err in its conclusions that the claims are infringed, that Appellants failed to prove that the claims would have been obvious and are not enabled, and that Appellants failed to prove that Group II claims are indefinite. We also hold that the district court erred in concluding that Group I claims have not been proven indefinite. Accordingly, we *affirm* the district court's judgments of infringement and no invalidity with respect to Group II claims, *reverse* its judgment of no invalidity with respect to Group I claims, and *remand*.[5]

COSTS

No costs.

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[5] We note that, according to the Orange Book, all of Teva's Copazone® patents expire on the same date: May 24, 2014. We remand for the district court to determine whether there exists any need to modify its injunction.

AFFIRMED-IN-PART, REVERSED-IN-PART AND REMANDED

APPENDIX B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., et al., Plaintiffs, v. SANDOZ INC., et al., Defendants.	08 Civ. 7611 (BSJ) (AJP)
TEVA PHARMACEUTICALS USA, INC., et al., Plaintiffs, v. MYLAN PHARMACEUTICALS INC., et al., Defendants.	09 Civ. 8824 (BSJ) (AJP) **Memorandum and Order**

BARBARA S. JONES
UNITED STATES DISTRICT JUDGE

Plaintiffs Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience,

Inc., and Yeda Research and Development Co. Ltd. (collectively, "Teva") filed suit for patent infringement and declaratory judgment against Defendants Sandoz Inc., Sandoz International GmbH, Novartis AG, and Momenta Pharmaceuticals, Inc. (collectively, "Sandoz").[1] Teva subsequently filed suit for patent infringement and declaratory judgment, with respect to the same patents, against Defendants Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (collectively, "Mylan") (collectively with Sandoz, "Defendants"). The two actions are now consolidated.

The issue before the Court is the proper construction of the nine patents-in-suit.[2] The nine patents contain a total of seventy-eight claims. All are related as continuation or divisional patents that claim priority to U.S. Patent Application Serial No. 08/344,248, filed November 23, 1994, which is a continuation-in-part of U.S. Patent Application Serial No. 08/248,037, filed May 24, 1994. The patents-in-suit also share a common specification.[3]

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[1] Teva voluntarily dismissed, without prejudice, their claims against Sandoz International GmbH and Novartis AG. (Dkt. 180 in 08 Civ. 7611 (BSJ) (AJP).)

[2] The nine patents are: 5,800,808 ("'808 patent"), 5,981,589 ("'589 patent"), 6,048,898 ("'898 patent), 6,054,430 ("'430 patent"), 6,342,476 ("'476 patent"), 6,362,161 ("'161 patent"), 6,620,847 ("'847 patent"), 6,939,539 ("'539 patent"), and 7,199,098 ("'098 patent").

[3] Accordingly, for ease of reference, unless noted otherwise, all citations to the specification are to the '808 patent specification.

BACKGROUND

Teva manufactures and markets Copaxone, a drug used to treat multiple sclerosis ("MS"). Sandoz and Mylan each filed an Abbreviated New Drug Application with the United States Food and Drug Administration seeking approval to manufacture and sell a generic version of Copaxone in the United States. Shortly thereafter, Teva filed separate suits against Sandoz and Mylan.

The active ingredient in Copaxone is glatiramer acetate, a composition of copolymer-1. The claims of the patents-in-suit pertain to copolymer-1 with particular molecular weight characteristics, methods of manufacturing copolymer-1 with such characteristics, and methods for treating MS using copolymer-1 with such characteristics.

The crux of both Defendants' claim construction argument is that the patent claims are indefinite because the patents fail to specify the type of molecular weight being claimed or the standards and conditions by which the claimed molecular weight should be determined. Sandoz previously moved for summary judgment on this basis. The Court denied Sandoz's motion. Mylan subsequently filed its own motion for a summary judgment finding of invalidity on the basis of indefiniteness under 35 U.S.C § 112. Because the Court finds the patent claims can be construed, Mylan's motion for summary judgment is DENIED.

LEGAL STANDARD

"[C]laim construction is a matter of law" decided by courts. Markman v. Westview Instruments, Inc., 52 F.3d 967, 97 9 (Fed. Cir. 1995) (en banc). "[T]he focus in construing disputed terms in claim language is not the subjective intent of the parties " Id. at 986. Courts must, rather, perform an "objective" inquiry into "what one of ordinary skill in the art at the time of the invention would have understood the term to mean." Id.

In Phillips v. AWH Corp., the Federal Circuit set forth the prevailing process for construing patent claims. 415 F.3d 1303 (Fed. Cir. 2005) (en banc). First, claim terms should "'generally [be] given their ordinary and customary meaning.'" Id. at 1312 (citations omitted). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." Id. at 1313 (citations omitted). Second, "because patentees frequently use terms idiosyncratically," in cases where "the meaning of a claim term as understood by persons of skill in the art is not immediately apparent," courts should look to "'sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean.'" Id. at 1314 (citation omitted). "Those sources include[,]" in the following order of significance, "'the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the

meaning of technical terms, and the state of the art.'" Id. (citations omitted).

Indefiniteness, like claim construction, "is a legal question." Young v. Lumenis, Inc., 492 F.3d 1336, 1344 (Fed. Cir. 2007) (citation omitted). Because patents are "presumed to be valid, the evidentiary burden to" prove indefiniteness "is one of clear and convincing evidence." Id. at 1345 (citation omitted). To satisfy Section 112's "definiteness requirement, the boundaries of the claim, as construed by the court, must be discernible to a skilled artisan based on the language of the claim, the specification, and the prosecution history, as well as her knowledge of the relevant field of art." Power-One, Inc. v. Artesyn Techs., Inc., 599 F.3d 1343, 1350 (Fed. Cir. 2010) (citation omitted). A claim is indefinite when it "is 'not amenable to construction or [is] insolubly ambiguous.'" Id. (citation omitted). "[A] claim is not indefinite merely because it poses a difficult issue of claim construction." Id. (citation omitted). "'[I]f the meaning of the claim is discernible, even though the task may be formidable and the conclusions may be one over which reasonable persons will disagree, the claim [is] sufficiently clear to avoid invalidity on indefiniteness grounds.'" Id. (citation omitted). In addition, "the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite." Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1379 (Fed. Cir. 2001) (citation omitted).

DISCUSSION

1. "Copolymer-1"

The term "copolymer-1" appears in all of the asserted claims. The specification describes "copolymer-1" as "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550)." ('808 patent at 1:32-37.) The "object" of the invention, according to the specification, is "to provide an improved composition of copolymer-1" with a lower average molecular weight and fewer higher molecular weight species. (Id. at 1:38-39; 1:64-2:14.)

Sandoz argues that while the final composition may have a lower molecular weight, the copolymer-1 claimed in the patents must be synthesized by starting with copolymer-1 that has an average molecular weight of 23,000 daltons. Sandoz contends that the patent teaches that the prior art (U.S. Patent No. 3,849,550 ("'550 patent")) results in the formation of a copolymer-1 mixture with a molecular weight of 23,000 daltons. Sandoz is wrong.

Example 1 in the specification describes preparation of copolymer-1, "according to" methods described in the '550 patent, that "had an average molecular weight of 12 KDa." (Id. at 2:53-55, 3:14-16.) As a result, a person of ordinary skill in the art would not read 23,000 daltons into the definition of copolymer-1, as Sandoz claims. See Phillips, 415 F.3d

at 1316 ("the specification necessarily informs the proper construction of the claims") (citation omitted).

Sandoz also argues that copolymer-1 should be construed as having a "random amino acid composition." Sandoz points to a statement in the prosecution history, where Teva distinguished the patents-in-suit from an earlier European patent application, EPA 0 383 620 ("'620 patent application"). Teva stated that "[t]he copolymer-1 [of the '620 patent application] is distinguished from copolymer-1 of [the patents-in-suit] insofar as [t]he copolymer-1 of the '620 application does not have a random amino acid composition." (Kramer Decl. Ex. 9 ('476 patent prosecution, Amendment Under 37 C.F.R. § 1.111, at 4) (Teva v. Sandoz claim construction).) From this statement, Sandoz concludes that the copolymer-1 in the patents-in-suit must be "random."

Sandoz provides only a sliver of Teva's response, however. Viewed in its entirety, Teva's statement is clear that the distinction was not based on randomness:

> The copolymer-1 of the '620 application does not have a random amino acid composition, but rather is derived from blocks of nucleotides, which results in copolymer-1 having arrangement of specific blocks of polypeptide sequences [S]ince the copolymer-1 of the present application is not composed [of] specific blocks of polypeptides sequences, it is clearly distinguished over the copolymer-1 disclosed in the '620 patent.

(Id.) The Court also accepts Teva's expert's (Dr. Gregory Grant) representation that a person of ordinary skill in the art would understand that while the copolymer-1 referred to in the patents-in-suit is not composed of specific blocks of polypeptides sequences, the sequence is not completely random given the chemical properties of the amino acids and their inherent reactivity to each other. (Grant Decl. ¶ 47 (Teva v. Sandoz claim construction).) Accordingly, the Court rejects Sandoz's argument that copolymer-1 should be construed as having a "random amino acid composition." See Phillips, 415 F.3d at 1318 (explaining that "extrinsic evidence in the form of expert testimony can be useful to a court for a variety of purposes, such as to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art") (citations omitted).

Teva, for its part, argues that the mixture of polypeptides should be construed to include the term "complex." Teva points to a statement by the patent examiner in the prosecution of the '098 patent, noting that copolymer-1 "is a complex mixture of polypeptides made by polymerizing alanine, glutamic acid, lysine and tyrosine in a molar ratio of approximately 6:2:5:1." (Jean Decl. Ex. 5 at TEV000308865 (Teva v. Sandoz claim construction).) "Such polymerization[,]" the patent examiner added, "results in an extremely complex mixture of products, varying both in molecular weight and amino acid sequence." (Id. at TEV000308866.)

As Defendants emphasize, however, the patent examiner made this remark, not Teva. The law

requires "the patentee to 'define precisely what his invention is.'" See Phillips, 415 F.3d at 1312 (citation omitted); cf. Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1124 (Fed. Cir. 2004) ("It is well settled that it is the applicant, not the examiner, who must give up or disclaim subject matter that would otherwise fall within the scope of the claims.") Here, neither the claims nor specifications refer to the mixture of polypeptides that make up copolymer-1 as "complex." Teva also did not refer to the mixture of polypeptides as "complex" at any point during the prosecution history. While the Court credits Teva's expert's opinion that a person of ordinary skill in the art would have understood copolymer-1 to be "complex" based on its nature and method of manufacture (Grant Decl. ¶¶ 48, 50 (Teva v. Sandoz claim construction), this understanding is not a basis for importing this characterization into the patent claims.

Teva also argues, based on the statement from the patent examiner recited above, that copolymer-1 should be construed to mean "non-uniform with respect to molecular weight and sequence." Although the patent examiner, not Teva, indicated that the mixture of polypeptides that make up copolymer-1 "vary[] both in molecular weight and amino acid sequence[,]" (Jean Decl. Ex. 5 at TEV000308866 (Teva v. Sandoz claim construction), this statement, unlike the term "complex," is not a characterization. Instead, it is a description of the copolymer-1 being claimed. In addition to the patent examiner's statement, Dr. Grant represents that a person of ordinary skill in the art "would have

understood that the mixture, as a whole, is non-uniform with respect to amino acid sequence as well as the number of amino acid residues." (Grant Decl. ¶ 57 (Teva v. Mylan claim construction).) The Court credits Dr. Grant's statement. See Phillips, 415 F.3d at 1318 ("expert testimony can be useful to provide background on the technology at issue") (citations omitted). In view of the patent examiner's description in the prosecution history and Dr. Grant's opinion, the Court accepts Teva's argument that copolymer-1 should be construed to mean, inter alia, "non-uniform with respect to molecular weight and sequence."

Lastly, Teva argues that copolymer-1 should be construed as being "synthesized by polymerization of suitably protected amino acid carboxyanhydrides." The patent specification specifically provides that copolymer-1 "is synthesized by chemically polymerizing the four amino acids." ('808 patent at 1:34-35.) Sandoz does not object to a construction similar to the one provided in the patent specification.[4] Mylan objects to this construction primarily on the basis that it addresses how the claimed copolymer-1 is made, not what it is. Although Mylan is technically correct, the Court agrees with Teva that an understanding of the process by which copolymer-1 is made is important to

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[4] Specifically, Sandoz does not object to a construction including "synthesized by chemically polymerizing the four amino acids (including N-carboxyanhydride and protected amino acids)." (Sandoz Opp'n at 22; see also '808 patent at 2:15-19 (describing copolymer-1 "prepared by methods known in the art, wherein the N-carboxyanhydrides of tyrosine, alanine, y-benzyl glutamate and E-N-trifluoro-acetyllysine are polymerized").)

the meaning one of ordinary skill in the art would ascribe to this term. (Grant Decl. ¶¶ 56-59 (Teva v. Mylan claim construction).) With respect to the polymerization being "suitably protected," Dr. Grant explains that "to avoid unwanted reactions during chemical synthesis, potentially reactive chemical groups"—particularly, the R-groups of some amino acids—"need to be modified not [to] interfere with peptide bond formation." (Grant Decl. ¶ 29 (Teva v. Sandoz claim construction).) "The process of chemical modification[,]" Dr. Grant explains, "is sometimes called 'protecting.'" (Id.) In view of Dr. Grant's explanation that this is what one of ordinary skill in the art would understand "suitably protected" to mean in the context of the copolymer-1 being claimed in the patents, the Court accepts Teva's proposed construction. See Phillips, 415 F.3d at 1318 ("expert testimony can be useful to provide background on the technology at issue [and] to explain how an invention works").

For the reasons provided above, the Court construes "copolymer-1" to mean: "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides."

2. "Polypeptides composed of" and "copolymers of"

The '539 patent claims "a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine." ('539 patent at 5:18-20.) Along similar

lines, the '098 patent claims "a mixture of copolymers of alanine, glutamic acid, lysine and tyrosine." ('098 patent at 5:42-43.) Although they make different arguments, both Defendants argue that "composed of" and "of" should be construed to exclude additional elements. Teva argues, by contrast, that these terms should be construed to mean "contains."

Terms "like 'composed of' and "of" are "'transition phases.'" AFG Indus., Inc. v. Cardinal IG Co., Inc., 239 F 3d 1239, 1244 (Fed. Cir. 2001). "When a claim uses an 'open' transition phrase, its scope may cover unrecited elements." Id. (citation omitted). "'[C]losed transition phrases[,]' by contrast, "exclude any ingredients not specified in the claim." Id. at 1245 (citations omitted). Courts "have consistently held that the word 'comprising' is an open transition phrase." Id. (citations omitted). "'[C]onsisting of'" has consistently been interpreted to be a closed transition phrase. Id. (citations omitted).

In AFG, the Federal Circuit explained that there is "little prece[illegible]t defining the term 'composed of.'" Id. The Court noted that a 1942 Court of Customs and Patent Appeals decision stated that "'composed of should be regarded as synonymous with 'consisting of.'" Id. (citation and internal quotation marks omitted). Since then, however, the court observed, the "phrase appears to have acquired a meaning somewhat more expansive than 'consisting of.'" Id. "[B]ased on the specification and other evidence before" the court in that case, the Federal Circuit found "that the term 'composed of is not completely closed." Id. Instead, "'composed of' should be interpreted in the same manner as

'consisting essentially of.' Under this approach, the transition phrase 'composed of' 'excludes ingredients that would materially affect the basic and novel characteristics of the claimed composition.'" Id. (citation omitted). Moreover, the Federal Circuit explained, "[t]he phrase is open to 'unlisted ingredients that do not materially affect the basic and novel properties of the invention.'" Id. (citation omitted). The same is true here.

First, as the specification indicates, copolymer-1 polypeptides are "synthesized by chemically polymerizing" suitably protected amino acid carboxyanhydrides. ('808 patent at 1:34-35.) The Court credits Dr. Grant's explanation that a person of ordinary skill in the art would understand that "such chemical polymerization would inherently result in polypeptides that contain at least some impurities besides the four amino acid residues. The impurities would include," Dr. Grant notes as an example, "amino acids having unremoved protecting groups and/or initiator groups." (Grant Decl. ¶ 52 (Teva v. Sandoz claim construction); see also id. ¶ 53.) While these impurities "are inevitably present in the polypeptides[,]" Dr. Grant adds, they "do not materially affect the underlying characteristics of the polypeptides." (Id. ¶ 52.) In view of Dr. Grant's explanation regarding how a person of ordinary skill in the art would understand the patent specification, the Court construes "composed of" and "of," in the context of the patents-in-suit, to mean "'consisting essentially of.'" See AFG, 239 F.3d at 1245.

For the reasons provided above, the Court construes "polypeptides composed of glutamic acid,

lysine, alanine and tyrosine" to mean "more than one polypeptide, each consisting essentially of glutamic acid, lysine, alanine and tyrosine residues." The Court construes "copolymers of alanine, glutamic acid, lysine and tyrosine" to mean "more than one polymer molecule, each consisting essentially of glutamic acid, lysine, alanine and tyrosine residues."[5] See id.

3. "Copolymer-1 Fraction"

The specification describes two ways of making the claimed copolymer-1. First, it describes fractions of copolymer-1 containing high molecular weight profiles. ('808 patent at 2:29-36.) Second, it describes preparing a copolymer-1 fraction directly upon removing the protection from the amino acids. (Id. at 2:36-40.) Mylan emphasizes that the term "copolymer-1 fraction" only appears in two claims ('476 patent at 6:8 and '161 patent at 6:1) and, in both instances, describes only the second process identified in the specification. Accordingly, Mylan argues, "copolymer-1 fraction" should be limited to the second process.

Mylan provides no basis, however, for ignoring the specification, which clearly identifies two ways of making the claimed copolymer-1. Indeed, after claim construction briefing, even Sandoz acknowledged that the specification describes two methods for making copolymer-1. (See Teva's Responsive Claim

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[5] In light of the Court's construction of the term "copolymers of," to the extent Mylan asks the Court to construe the term "copolymer-1 composition" to exclude copolymer-1 with other substances, the Court rejects Mylan's proposed construction.

Construction Br. at p. 17-18.) In view of the fact that "[t]he specification is the primary basis for construing the claims[,]" the Court rejects Mylan's proposed construction of "copolymer-1 fraction." See Phillips, 415 F.3d at 1315 (citation omitted). The term "copolymer-1 fraction," in the context of the patents-in-suit, means "a portion of a copolymer-1 mixture having a narrower molecular weight distribution than the starting protected copolymer-1 mixture."

4. The "Molecular Weight" Limitations

Sandoz and Mylan argue that every use of the term "molecular weight" in the patent claims is indefinite. The Court disagrees.

A. "Average Molecular Weight"

Outside the context of copolymer-1 mixtures, there is virtually no dispute that "molecular weight" means the sum of the atomic weights of the atoms making up a molecule.[6] (See Sandoz Opening Claim

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[6] Sandoz concedes that copolymer-1 mixtures are made up of individual molecules, but argues that the patents-in-suit are indefinite because it is not possible to determine the molecular weight of an individual copolymer-1 molecule. (Sandoz Reply Claim Construction Br. at 2.) Only groups of copolymer-1 molecules can be measured, according to Sandoz. Thus, while some claims do not use the AMW or molecular weight, Sandoz argues, they necessarily refer to groups of molecules and, as a result, AMW.

The Court rejects this argument in view of Sandoz's expert's concession that when the term "molecular weight" is used in reference to species of copolymer-1 polypeptides, it refers to the molecular weights of the individual molecules and that, in this context, the term "molecular weight" has its meaning. (Blessing

Construction Br. at 9 (conceding that Teva's proposed construction "may be an acceptable definition for 'molecular weight' when referring to a small molecule, such as water, in which every molecule has the same molecular weight"); see also Grant Decl. ¶¶ 24, 54 (Teva v. Sandoz claim construction).) Because complex non-uniform mixtures, such as copolymer-1, often include molecules of varying weights, however, the molecular weight of such mixtures cannot be characterized by the molecular weight of any single species. (Id. ¶ 36.) "The most precise way of describing the molecular weight of such" mixtures, according to Dr. Grant, "is a complete molecular weight distribution." (Id.) For practical purposes, "the molecular weight of a polymer is often expressed in a single, average molecular weight" ("AMW"). (Id.)

The parties agree that for mixtures such as copolymer-1, several different types of AMW can be determined, including number average molecular weight ("Mn"), weight average molecular weight ("Mw"), z average molecular weight ("Mz"), viscosity average molecular weight ("Mv"), and peak average molecular weight ("Mp").[7] (See Ryu Decl. ¶¶ 23, 41 (Teva v. Mylan claim construction); see also Grant Decl. ¶¶ 38-39 (Teva v. Sandoz claim construction).)

Decl. Ex. 1 (Dr. Frantisek Svec Dep. at 125-26, 132, 136, 264 (Teva v. Sandoz claim construction).)

[7] Dr. Chang Ryu, Mylan's expert points out that Mp is not, in fact, "an average molecular weight but rather a point taken from a plot of the molecular weight distribution curve." (Ryu Decl. ¶ 41.) In the end, though, he concedes that molecular weight at the peak of the molecular weight distribution curve is sometimes reported as a single AMW. (Id.)

In view of the fact that AMW has no "ordinary and customary meaning" in the context of copolymer-1, the Court looks to "'the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence.'" See Phillips, 415 F.3d at 1313, 1314 (citations omitted).

i. Specification, Prosecution History, and Extrinsic Evidence

The "'claims themselves'" are silent as to the meaning of AMW. Accordingly, the Court looks to "'the specification, the prosecution history, and extrinsic evidence.'" Id. at 1314 (citations omitted). In Phillips, the Federal Circuit explained that the specification is usually "'dispositive; it is the single best guide to the meaning of a disputed term.'" Id. at 1315 (citation omitted). "The close kinship between the written description and the claims is enforced by the statutory requirement that the specification describe the claimed invention in 'full, clear, concise, and exact terms.'" Id. at 1316 (quoting 35 U.S.C. § 112, para. 1).

Here, the specification expressly describes use of a method called size exclusion chromatography ("SEC"), in which a sample is passed through a gel-filled column. ('808 patent at 3:3-8.) SEC, which "was well understood at the time the patent applications were filed in 1994[,]" according to Dr. Grant, is typically "performed by passing a solution of a polymer down a column packed with a porous gel." (Grant Decl. ¶ 40 (Teva v. Sandoz claim construction).) The gel contains pores of varying sizes into which some, but not all, of the copolymer molecules may fit. (Id.) When a polymer sample is

run through the size exclusion column, Dr. Grant explains, the larger molecules that cannot fit in all of the pores go ground them and come out of the column earlier. (Id.) Smaller molecules, by contrast, diffuse more easily into the pores, thus taking a longer route through the gel and coming out later. (Id.) As a sample comes out of the column, the polypeptides are measured by ultraviolet ("UV") light absorption. (Id. ¶ 41.) The amount of UV light absorbed is proportional to the amount of polypeptide present. (Id. n.12.) SEC generates a chromatogram "by plotting UV absorbance versus elution volume or retention time. The peak on the chromatogram corresponds to a fraction that contains the largest amount of polymer, the molecular weight of which is the peak or 'peak average' molecular weight." (Id. ¶ 41.) Thus, Teva (and Dr. Grant) conclude, Mp can be read from the chromatogram generated by SEC without any "further calculation" and would be understood by a person of ordinary skill in the art to be the presumed meaning of AMW in the context of the patents-in-suit. (Id. ¶ 61.)

Dr. Grant adds that while "[p]eak molecular weight can be obtained directly from the chromatogram and the calibration curve, further data manipulation and calculation is needed to calculate either the weight average molecular weight or the number average molecular weight." (Id.) Because "[t]he specification does not describe the calculation of the average molecular weight," a person of ordinary skill in the art would have understood, according to Dr. Grant, that the AMW "referred to is a peak molecular weight." (Id.)

The Court credits and accepts all of Dr. Grant's opinions regarding SEC. See Phillips, 415 F.3d at 1318 ("expert testimony can be useful ... to provide background on the technology at issue [and] to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art") (citations omitted).

Example 1 in the specification describes a method for measuring the AMW of a sample of copolymer-1 using SEC. ('808 patent at 3:3-8.) Teva argues, and the Court agrees, that a person of ordinary skill in the art would understand that Figure 1 in the specification relates to Example 1. Figure 1 depicts three molecular weight distributions curves. ('808 patent at Fig. 1.) Two have an AMW of 7.7 kilodaltons ("kDa"). (Id.) The other has an AMW of 12.0 kDa. (Id.) The specification states that Figure 1 "displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa." (Id. at 1:57-59.) Dr. Grant explains that a person of ordinary skill in the art would understand that Figure 1 does not represent raw data off of a size exclusion column, but, rather, would understand that the SEC apparatus and its UV detector would generate a chromatogram, which would have to be converted into the graph shown in Figure 1 in the patent. (Grant Decl. ¶¶ 41, 62 (Teva v. Sandoz claim construction).)

Finding that the samples described in Example 1 correspond to the data described in Figure 1, a person of ordinary skill in the art would understand, according to Dr. Grant, that the listed AMWs fall

approximately at the peaks of the curves. (Id. ¶ 62.) A person of ordinary skill in the art would also understand, Dr. Grant explains, "that the process of transferring the data from the chromatogram would likely cause the peak on each curve to shift slightly." (Id.) Thus, a person of ordinary skill in the art would understand that any discrepancy between the peak values read from the chromatogram (7.7 kDa and 12.0 kDa) and the peak of Figure 1 is merely a by-product of the process by which the data from the chromatogram would have been used to generate Figure 1. (Id.) The Court credits all of Dr. Grant's explanation regarding Example 1 and Figure 1. See Phillips, 415 F,3d at 1318.

In addition to the specification, the prosecution history also indicates AMW refers to Mp in the context of the patents-in-suit. The prosecution history, which, along with the specification, is referred to as "'intrinsic evidence,' consists of the complete record of the proceedings before the [Patent and Trademark Office ("PTO")] and includes the prior art cited during the examination of the patent." Id. at 1317 (citation omitted). The prosecution history, like the specification, "provides evidence of how the PTO and the inventor understood the patent." Id. (citation omitted). Since "the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation," however, "it often lacks the clarity of the specification and thus is less useful for claim construction purposes." Id. (citations omitted). Here, the prosecution history is just as useful as the specification.

The term "average molecular weight" was first used during the prosecution of the '539 patent. Teva stated it sought claims to "[a] copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons." (Crystal Decl. Ex. 13 at TEV000304783 (Teva v. Mylan claim construction).) The patent examiner rejected the claims directed to "average molecular weight" as indefinite on the basis that the PTO could not determine what average was being claimed:

> Where a claimed value varies with its method of measurement and several alternative methods of measurement are available, the claimed value is indefinite without knowing which method of measurement was used. Honeywell Intl., Inc. v. Intl. Trade Commn., 341 F.3d 1332, 1340 (Fed. Cir. 2003). Accordingly, the term "average molecular weight" is indefinite since its method of measurement is not specified, i.e., number average molecular weight, weight average molecular weight, average molecular weight as determined by light scattering, etc.

(Crystal Decl. Ex. 12 at TEV000304691 (Teva v. Mylan claim construction).)

In response to the rejection, Teva pointed to the specification to explain that a person of ordinary skill in the art would understand AMW to mean "peak average molecular weight":

> According to the examiner, the term "average molecular weight" is indefinite. Applicants respectfully disagree. One of ordinary skill in the art, upon reviewing the specification, would understand that "average molecular weight" refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1, which is "% of the total mass" versus "molecular weight." As shown in Figure 1, the "average molecular weight" is 7.7 kDa for the separated copolymer-1 ("Batch A") described in Example 1, and 12.0 kDa for the unseparated copolymer-1

(Crystal Decl. Ex. 13 at TEV000304803 (Teva v. Mylan claim construction).) The patent examiner accepted Teva's explanation and issued a Notice of Allowability, specifically noting Teva's "remarks and amendments." (Crystal Decl. Ex. 14 (Teva v. Mylan claim construction).)

In situations like this, where a patent examiner has specifically raised an indefiniteness objection and the issue has been resolved to the patent examiner's satisfaction, " [t]hero is a 'heavy presumption against [a party] arguing that the patents and claims do not comply with 35 U.S.C. § 112." See Mas-Hamilton Grp. v. LaGard, Inc., 21 F Supp. 2d 700, 717 (E.D. Ky. 1997) (citations omitted).

ii. Defendants' Indefiniteness Arguments

a. Specification

As explained above, indefiniteness must be proven by "clear and convincing evidence." See Young, 492 F.3d at 1345 (citation omitted). Defendants primarily attempt to meet this burden by poking holes in the specification, the prosecution history, and Dr. Grant's explanation. Ultimately, Defendants fail to carry their burden.

Mylan attacks the specification on several fronts. First, it argues that the specification teaches away from Mp by referencing a 1971 publication by Dr. Dvora Teitelbaum. The publication reports an AMW for copolymer-1 of 23 kDa, determined by ultracentrifugation. (Cornish Decl. Ex. P, at 244.) Ultracentrifugation, according to Mylan's expert, Dr. Chang Ryu, cannot provide Mp. (Ryu Decl. ¶ 39.) While Mylan is correct that the patent references the Teitelbaum publication, its argument fails because the specification itself makes no reference to ultracentrifugation. Instead, it describes only the use of SEC. ('808 patent at 3:4-8.) Mp is the only AMW provided directly by SEC without "further data manipulation and calculation." (Grant Decl. ¶ 70 (Teva v. Mylan claim construction).) Accordingly, a person of ordinary skill in the art would not conclude that the specification does not refer to Mp by virtue of the reference to the Teitelbaum publication.

Second, although SEC can provide Mp, this disclosure is insufficient, Mylan argues, in view of the fact that it can also provide Mw and Mn. (Ryu Decl. ¶ 41.) This argument fails because, as explained above, Mp is the only type of AMW that can be provided directly by SEC without "further data manipulation and calculation." (Grant Decl.

¶ 70 (Teva v. Mylan claim construction).) Since the patents-in-suit do not disclose any additional calculations, the Court credits Dr. Grant's representation that a person of ordinary skill in the art would understand that AMW means Mp. (See id.)

Lastly, Mylan concedes that Mp may be derived from Figure 1, but argues that Figure 1 does not show peaks of either 7.7 kDa or 12.0 kDa. (Ryu Decl. ¶ 42.) This argument fails because, as Dr. Grant explained, a person of ordinary skill in the art would understand, based on Example 1's reference to SEC, that Figure 1 was created by transforming data from a chromatogram to the curves depicted in Figure 1. (Grant Decl. ¶¶ 44-53 (Teva v. Mylan claim construction); see also Grant Decl. ¶ 62 (Teva v. Sandoz claim construction).) A person skilled in the art would understand, according to Dr. Grant, "that the process of transferring the data from the chromatogram would likely cause the peak on each curve to shift slightly." (Grant Decl. ¶ 62 (Teva v. Sandoz claim construction); see also Grant Supp. Decl. ¶7 (Teva v. Mylan claim construction).) As a result, the fact that the peaks in Figure 1 do not match the listed AMWs precisely would not dissuade a person of ordinary skill in the art from concluding that AMW refers to Mp in the context of the patents-in-suit.

Sandoz, for its part, devotes substantial energy to discrediting Dr. Grant and his explanation regarding how one of ordinary skill in the art would understand Figure 1. Sandoz relies almost exclusively, however, on unsubstantiated attorney-

argument. The Court finds that Sandoz's unsubstantiated attorney-argument is insufficient to cast doubt on Dr. Grant's opinions, which, as explained above, the Court credits and accepts. See Invitrogen Corp. v. Clontech Labs., Inc., 429 F.3d 1052, 1068 (Fed. Cir. 2005) ("Unsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony.")

b. Prosecution History

Sandoz and Mylan both devote considerable attention to the prosecution history. While prosecuting the patents, Teva, Defendants contend, proffered contradictory definitions of AMW. First, Defendants point out, during the prosecution of the '898 patent, the patent examiner rejected Teva's claims on the basis that it was "unclear what constitutes a molecular weight 'profile'; there are many possible determinations including polydispersity, absolute weight ranges, distribution by light scattering, etc., and the specification provides no guidance as to when a given 'profile' will be within the scope of the claims and when it will not." (Kramer Decl. Ex. 6 at pp. 2-3 (Office Action Summary) (Teva v. Sandoz claim construction).) Teva responded, "[t]he molecular weight profile represents the percentage of copolymer-1 or trifluoroacetyl copolymer-1 having a molecular weight above a given amount." (Id. at p. 5 (Amendment Under 37 C.F.R. 1.111).) Teva added that "[i]t may be determined using any method known to those in the art." (Id.)

Second, during the prosecution of the '847 patent, the patent examiner rejected Teva's claims on the ground that "[t]he term 'average' molecular weight ... is meaningless as a limitation without specifying its basis, e.g., weight average molecular weight, number average molecular weight, etc. (The values of the polymer molecular weights will vary according to the type of molecular weight, as anyone skilled in the art will appreciate)." (Kramer Decl. Ex. 7 at p. 3 (Office Action Summary) (Teva v. Sandoz claim construction).) Teva responded, "[o]ne of ordinary skill in the art could understand that kilodalton units implies a weight average molecular weight." (Id. at p. 3 (Amendment).)

Finally, as explained above, during the prosecution of the '539 patent, in response to an indefiniteness objection from the patent examiner, Teva explained that a person "of ordinary skill in the art, upon reviewing the specification, would understand that 'average molecular weight' refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1." (Crystal Decl. Ex. 13 at TEV000304803 (Teva v. Mylan claim construction).) In view of these inconsistent prosecution history statements, Defendants argue, a person of ordinary skill in the art would not know what type of AMW Teva was claiming.

While Defendants are correct regarding what Teva said in each instance, upon inspection, their argument fails to pass muster. First, with respect to the '898 patent prosecution statement, as Teva points out, the statement does not specifically discuss the term "average molecular weight." As a

result, a person of ordinary skill in the art would not look to it to determine what AMW referred to in the context of the patents-in-suit. Second, with respect to the statement made during the prosecution of the '847 patent, Teva admits its statement—"kilodalton units implies a weight average molecular weight"—was incorrect. Because the statement was incorrect, a person of ordinary skill in the art would not rely on it. As Sandoz's expert, Dr. Frantisek Svec, explained, "each type of 'average molecular weight' can use the dalton." (Svec Decl. ¶ 33.) Understanding that the statement is wrong (see Grant Decl. ¶ 64 (Teva v. Sandoz claim construction), a person of ordinary skill in the art would not conclude that AMW, in the context of the patents-in-suit, "implies weight average molecular weight." (Kramer Decl. Ex. 7 at p. 3 (Amendment).)

In view of the problems with the earlier prosecution statements, the Court agrees with Teva that a person of ordinary skill in the art would accept the '539 patent prosecution statement—the only statement that defined AMW directly—as proof of what Teva meant by AMW. Anticipating this finding, Mylan argues that because seven of the nine patents-at-issue issued before Teva clarified what it meant by AMW, Teva's remarks cannot be applied retroactively to the earlier issued patents. Mylan cites Biovail Corp. Int'l v. Andrx Pharmaceuticals, Inc., 239 F.3d 1297 (Fed. Cir. 2001), in support of this argument. Biovail, however, does not address retroactive application of a later-issued patent's prosecution history to an earlier issued, related patent. Instead, the Federal Circuit held, "'[w]hen multiple patents derive from the same initial

application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation.'" Id. at 1301 (emphasis added) (citations omitted). Since the specification of the first patent indicated AMW refers to Mp (Example 1 with its discussion of SEC and Figure 1), and nothing from the prosecutions of the '898 patent or '847 patent would undermine this understanding for a person of ordinary skill in the art, nothing from one of the earlier issued patents taints the '539 patent prosecution history's clear statement regarding Mp.

In addition, in Microsoft Corp. v. Multi-Tech Systems, Inc., the Federal Circuit held that the prosecution history of a later issued, related patent is relevant and may be used to construe the same term in a patent that has already issued. 357 F.3d 1340, 1350 (Fed. Cir. 2004). Accordingly, Teva's statement during the prosecution of the '539 patent is relevant to the earlier issued patents.

c. Extrinsic Evidence

The lone argument Defendants make regarding extrinsic evidence, apart from their criticism of Dr. Grant, which was addressed above, is that neither of the named inventors who were deposed testified that AMW means Mp in the context of the patents-in-suit.[8] This argument does not pass muster because Mylan does not allege—much less establish—that either of the two named inventors

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[8] Inventor testimony constitutes extrinsic evidence. See Phillips, 415 F.3d at 1317 (citations omitted).

who were deposed—Dr. Michael Sela and Dr. Ruth Arnon—is a person of ordinary skill in the art of determining molecular weight. Furthermore, an inventor's "'subjective intent'" regarding "'the scope of a claim'" "'is of little or no probative weight.'" See Howmedica Osteonics Corp. v. Wright Med. Tech., Inc., 540 F.3d 1337, 1346 (Fed. Cir. 2008) (citation omitted). As the Federal Circuit explained in Howmedica, while "an inventor understands the invention[,]" that does not mean that he or she "understand[s] the claims, which are typically drafted by the attorney prosecuting the patent application." Id. at 1346-47.

iii. Standards and Conditions

Defendants argue that even if a person of ordinary skill in the art could determine that AMW refers to Mp in the context of the patents-in-suit, the patents are still indefinite. According to Defendants, a skilled artisan would not know whether his copolymer-1 was inside or outside Teva's claims because the patents do not identify the standards and conditions a person of ordinary skill in 1994 should use for determining the claimed AMW value. Mylan's experts, Dr. Jerard Hurwitz and Dr. Ryu, contend that for any results to be valid and reproducible, the SEC standards (markers) and running conditions Teva used had to be disclosed. (Hurwitz Decl. ¶¶ 17-24; Ryu Decl. ¶ 51.) The necessary information includes, Mylan's experts argue, the chemical properties of the buffer (such as the pH, temperature, and salt concentration) as well as the physical parameters of the instrumentation (such as flow rate). (Hurwitz Decl. ¶¶ 17-24; Ryu

Decl. ¶ 51.) Altering these conditions, according to Dr. Hurwitz and Dr. Ryu, can have a substantial effect on the AMW determination, and without knowing which conditions to use, a person of ordinary skill in the art would not be able to tell whether he or she was infringing. (Hurwitz Decl. ¶¶ 17-24; Ryu Decl. ¶¶ 51-54.) Dr. Hurwitz and Dr. Ryu also assert that calibration standards can dramatically affect the AMW value. (Hurwitz Decl. ¶¶ 22-23; Ryu Decl. ¶ 51.)

Defendants argue that Teva's proposed construction of AMW as Mp "detected using an appropriately calibrated suitable gel filtration column" is indefinite because the patents are silent regarding what "appropriately calibrated" and "suitable" mean. Absent objective standards for determining what is "appropriately calibrated" and "suitable," a person of ordinary skill in the art would have no way of knowing whether he or she infringed Teva's AWM claims, according to Defendants.

Teva's experts, Dr. Grant and Dr. Paul Dubin, rebut Defendants' arguments on the basis that a person of ordinary skill in the art, since 1994, would independently be capable of selecting appropriate SEC standards and conditions to determine if a product matches Teva's claimed molecular weights. According to Dr. Grant, a skilled artisan "would have understood that [he or she] could use more than one set of standards and/or conditions to obtain accurate results, i.e., that their analysis was not limited to the use of a single set of standards and conditions." (Grant Supp. Decl. ¶ 12 (Teva v. Mylan claim construction); see id. ¶ 14 ("There is not one unique

set of standards that must be used to accurately measure the molecular weight of any particular sample."); id. ¶ 23 ("There is not one unique set of SEC conditions that must be used to accurately measure the molecular weight of any particular sample."); id. ¶ 24 ("there is no unique set of SEC standards and conditions that must be used in order to obtain accurate and consistent molecular weight results for a given polymer").)

First, with respect to the standards, a person of ordinary skill in the art would understand, Dr. Grant explains, that any standard with similar hydrodynamic volume as the polymer being measured would be sufficient. (Id. ¶ 14.) A person skilled in the art "would have known that they could use either self-standards or existing commercial standards in conjunction with universal calibration in order to obtain an accurate molecular weight. The use of both self-standards and universal calibration was well known to persons of ordinary skill in the art in 1994." (Id. (citations omitted); see also Dubin Decl. ¶¶ 30-32, 52-61 (Teva v. Mylan claim construction) (explaining that a person of ordinary skill would have been able to use a universal calibration method, in addition to the use of self-standards, to accurately characterize samples of copolymer-1 or its fractions).) A skilled artisan would also understand, according to Dr. Grant, that the use of appropriate standards would produce the same or similar results, even if the standards were not the same. (Grant Supp. Decl. ¶¶ 23-24 (Teva v. Mylan claim construction).)

Second, with respect to the conditions, Dr. Grant explains that a person of ordinary skill in the art

"would have known how to select and adjust conditions such as column packing, column dimensions, sample volume, flow rate, pH and salt concentration" in the absence of "such conditions (or the calibration standards) being set forth in detail." (Grant Supp. Decl. ¶ 20 (Teva v. Mylan claim construction).) The skilled artisan would also have known, Dr. Grant adds, "that samples and standards should be treated under the same conditions." (Id. (citation omitted).) In the event inappropriate conditions were selected, according to Dr. Grant, a person of ordinary skill in the art would recognize that fact and adjust the conditions accordingly. (Id. ¶ 21.)

The Court credits and accepts Dr. Grant's and Dr. Dubin's explanation regarding the calibration standards and test conditions. In addition, to the extent that determining appropriate standards and conditions may have required some experimentation, as the Federal Circuit explained in Exxon Research, "the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite." 265 F.3d at 1379 (citation omitted).

Finally, Defendants' reliance on Honeywell Int'l, Inc. v. Int'l Trade Commission is misplaced. 341 F.3d 1332 (Fed. Cir. 2003). In Honeywell, infringement turned on the method of sample preparation. The Federal Circuit found Honeywell's claims were indefinite because "neither the claims, the written description, nor the prosecution history reference[d] any of the four sample preparation methods." Id. at 1339. In addition, the method

advanced by Honeywell "was not published" and "[t]he only written description ... in the record [was] a confidential Honeywell document." Id. at 1336.

Here, by contrast, the specification expressly describes use of SEC by a calibrated gel filtration column to measure AMW (See '808 patent at 3:4-8.) Based on this reference (along with Figure 1 and Teva's statements during the prosecution of the '539 patent), a person of ordinary skill in the art would understand that AMW refers to Mp. Thus, unlike in Honeywell, the patents-in-suit provide more than adequate instruction regarding how one skilled in the art should construe AMW and calculate it. See Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc., 554 F.3d 1010, 1022 (Fed. Cir. 2009) (finding "Honeywell does not control where several methods for calculating reduction in bacterial density are available but the specification discloses one particular method"); see also Oakley, Inc. v. Sunglass Hut Int'l, 316 F.3d 1331, 1341 (Fed. Cir. 2003) (noting that "a patentee need not define his invention with mathematical precision in order to comply with the definiteness requirement") (citation omitted). To the extent a skilled artisan would need to select appropriate calibration standards and test conditions, as explained above, "the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite."[9] See Exxon Research & Eng'g Co., 265 F. 3d at 1379 (citation omitted).

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[9] To the extent Mylan argues that the disputed claim terms that reference percentages of copolymers, polypeptides, or species (e.g., "wherein over 75% of the polypeptides of the

iv. Sandoz's Supplemental Claim Construction

After the Court denied Sandoz's motion for a summary judgment finding of invalidity on the basis of indefiniteness, Sandoz sought leave to file a supplemental claim construction brief. The Court granted Sandoz's request. In its supplemental claim construction brief, Sandoz argues that if the Court construes AMW to mean Mp, the Court should adopt a construction that defines what constitutes an "appropriate" calibration and what is a "suitable" gel filtration column. Sandoz asks the Court to include the following limitation: "peak molecular weight (Mp) as determined using a Superose 12 gel filtration column with conventional column preparatory methods, run conditions, and calibration standards that were commercially available prior to May 1994." Sandoz asserts that these constraints on the meaning of AMW come from the specification and are supported by Dr. Dubin's deposition testimony.

First, with respect to the specification, Sandoz points to the "Molecular Weight Analysis" portion of the specification, which states that "[t]he molecular

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mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons" ('539 patent at 5:65-6:2)) are indefinite because they fail to specify how molecular weight is to be determined and the standards and conditions to be applied, in view of the Court's findings above, the Court rejects Mylan's argument that these percentage claim terms are indefinite.

Because Mylan's argument that the term "molecular weight profile" is indefinite is also based on Teva's alleged failure to disclose the necessary standards and conditions, the Court rejects this argument, as well.

distribution of ... 2 batches was determined on a calibrated gel filtration column (Superose 12)." ('808 patent at 3:6-8.) Based on this portion of the specification, Sandoz contends a person of ordinary skill in the art would use a Superose 12. Second, with respect to Dr. Dubin, Sandoz highlights his deposition testimony in response to a question regarding whether Superose 12 is the only column that should be used to determine copolymer-1's AMW. Dr. Dubin replied: "For analyzing copolymer-1 in the context of the claims, it's evidently the best. So it's the only one in the sense that the choice of the others would be more likely to lead to ambiguous or imprecise results." (Kramer Decl. Ex. A, at 80:21-25 (Teva v. Sandoz supplemental claim construction).)

The Court rejects Sandoz's proposed construction. With respect to the Superose 12 column reference in the specification, the Federal Circuit "has consistently adhered to the proposition that limitations appearing in the specification will not be read into claims." Intervet Am., Inc. v. Kee-Vet Labs., Inc., 887 F.2d 1050, 1053 (Fed. Cir. 1989); see also Gart v. Logitech, Inc., 254 F.3d 1334, 1342-43 (Fed. Cir. 2001) (explaining that it is "improper[to] add a limitation appearing in the specification but not appearing in the unambiguous language of the claim") (citations omitted). Moreover, "[w]hile a court may look to the specification and prosecution history to interpret what a patentee meant by a word or phrase in a claim, extraneous limitations cannot be read into the claims from the specification or prosecution history." Bayer AG v. Biovail Corp., 279 F.3d 1340, 1348 (Fed. Cir. 2002) (citations omitted).

Here, the specification's reference to the Superose 12 column was merely an example of a gel filtration column that could be used to determine molecular weight distribution using SEC. Nothing in the specification requires use of a Superose 12 column. Because "a court may not read into a claim a limitation from a preferred embodiment, if that limitation is not present in the claim itself[,]" see id., there is no basis for reading into the claims use of the Superose 12 column.

In regard to Dr. Dubin's testimony, as Teva points out, he merely testified that a Superose 12 column is preferred. (See Kramer Decl. Ex. A, at 70:2-6 (Teva v. Sandoz supplemental claim construction) ("Other columns for aqueous size-exclusion chromatography were available in 1994, but one of ordinary skill in the art would understand that Superose 12 would be the best selection."); id. at 75:4-9 ("Understanding that the task was to obtain accurate molecular weight measurements on copolymer-1, a person of ordinary skill in the art would have known that of the columns available then, Superose 12 would have been the best choice.").) As a preferred embodiment identified by an expert, there is no basis for importing use of a Superose 12 column on account of Dr. Dubin's deposition testimony. See Bayer AG, 27 9 F. 3d at 1348; see also Riverwood Int'l Corp. v. R.A. Jones & Co., Inc., 324 F.3d 1346, 1358 (Fed. Cir. 2003) (explaining that "extrinsic evidence 'may not be used to vary or contradict the claim language' or 'import of other parts of the specification'") (citation omitted).

Because there is no basis for limiting the AMW to mean "peak molecular weight (Mp) as determined using a Superose 12 gel filtration column," the Court need not reach the additional limitations Sandoz seeks to impose with the use of a Superose 12 column—i.e., "conventional column preparatory methods, run conditions, and calibration standards that were commercially available prior to May 1994."

v. Construction

For the reasons provided above, the Court construes the term "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column."[10] Because the term "average molecular weight" is "'amenable to construction'" and not "'insolubly ambiguous[,]'" Mylan's motion for summary judgment on the basis of indefiniteness is DENIED. See Power-One, Inc., 599 F.3d at 1350 (citation omitted).

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[10] In view of the Court's findings above, to the extent Defendants contend "molecular weight" is indefinite when referring to copolymer-1, as Mylan's own expert concedes, "[i]n 1994, if a person of ordinary skill read that copolymer-1 has a molecular weight, he or she would assume that the writer intended 'average molecular weight.'" (Ryu Decl. ¶ 21.) Accordingly, in the context of the patents-in-suit, "copolymer-1 having a molecular weight" means "copolymer-1 having a peak molecular weight detected using an appropriately calibrated suitable gel filtration column."

5. "Weight Average Molecular Weight Less Than 10 Kilodaltons"

In its supplemental claim construction brief, Sandoz also argues that irrespective of whether the patents-in-suit refer to Mp, the prior art '550 patent refers to weight average molecular weight. Since Teva obtained the patents-in-suit by arguing that its invention has a lower molecular weight than the '550 patent, which, Sandoz contends, had a minimum weight average molecular weight of 10 kilodaltons, the patents-in-suit must be construed to have a weight average molecular weight of less than 10 kilodaltons.

The Court begins, as it must, by noting that none of the claims themselves expressly limit the patents-in-suit to copolymer-1 with weight average molecular weight less than 10 kilodatons. See Phillips, 415 F.3d at 1312 ("It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'") (citations omitted). The specifications also do not limit the patents-in-suit to copolymer-1 with weight average molecular weight less than 10 kilodatons. See id. at 1315 ("The specification is the primary basis for construing the claims.") (citation omitted).

Turning to the prosecution history, as the Federal Circuit explained in Purdue Pharma L.P. v. Endo Pharmaceuticals Inc., " [u]nder the doctrine of prosecution disclaimer, a patentee may limit the meaning of a claim term by making a clear and unmistakable disavowal of scope during prosecution." 438 F.3d 1123, 1136 (Fed. Cir. 2006) (citations omitted); see also Sorensen v. Int'l Trade

Comm'n, 427 F.3d 1375, 1378 (Fed. Cir. 2005) ("to disavow claim scope, a patent application must clearly and unambiguously express surrender of subject matter during prosecution") (citation omitted). Here, in response to an obviousness rejection, Teva distinguished the prior art '550 patent on the following basis: "the cited ['550 patent] reference teaches a minimum molecular weight of 10 kilodaltons. In contrast, claim 20 requires a copolymer-1 having a molecular weight of about 5 to 9 kilodaltons. The cited ['550 patent] reference does not teach or suggest obtaining the claimed molecular weight fraction of claim 20 "[11] (Kramer Decl. Ex. 11 at p. 4 (Amendment Under 37 C.F.R. § 1.111) (Teva v. Sandoz claim construction).)

This statement and several others like it do not "clearly and unambiguously express surrender of" copolymer-1 with a weight average molecular weight greater than 10 kilodaltons. See Sorensen, 427 F.3d at 1378 (citation omitted). As Teva emphasizes, the statement itself does not use the term "weight average molecular weight." In addition, to the extent Sandoz contends the '550 patent refers to weight average molecular weight, Sandoz concedes that the patent itself does not use that term. As a result, it resorts to confidential deposition testimony from two of the named inventors of the '550 patent— Dr. Arnon and Dr. Sela. Because, as Teva argues, this deposition testimony is confidential and is not available to one of ordinary skill in the art, even today, the Court does not consider it. See Markman, 52 F.3d at 986 (courts must conduct an "objective"

[11] Teva made identical or similar statements during the prosecution of several of the other patents-in-suit.

inquiry into "what one of ordinary skill in the art at the time of the invention would have understood the term to mean").

Lastly, Sandoz cites a 1971 article by Dr. Teitelbaum that was referred to during the prosecution of the '550 patent as proof that the average molecular weights in the '550 patent were determined using ultracentrifugation. Both Dr. Grant and Dr. Ryu agree, however, that ultracentrifugation can provide weight average molecular weight or z-average molecular weight. (See Kramer Decl. F (Grant Dep. at 290-91) (Teva v. Sandoz supplemental claim construction); see also Ryu Decl. ¶ 39 (Teva v. Mylan claim construction).) Even assuming, arguendo, Sandoz is correct that the '550 patent prosecution history reference to the Teitelbaum article is sufficient to establish that the molecular weight claimed there was calculated using ultracentrifugation—a finding the Court is not making—without any evidence the '550 patent referred to weight average molecular weight as opposed to z-average molecular weight, the Court cannot make a determination regarding the type of AMW referred to in the '550 patent. Accordingly, on the record before it, the Court cannot construe the patents-in-suit as being limited to weight average molecular weights of less than 10 kilodaltons.

6. "Toxicity"

Example 2 of the specification is titled, "Toxicity Analysis." ('808 patent at 3:20-4:27.) The specification identifies an "In Vivo" test and an "In Vitro" test. (Id.) The in vivo test addresses "toxicity" in terms of a mouse mortality test. (Id. at 3:21-45.)

The in vitro test addresses "toxicity" in terms of a Rat Basophilic Leukemia ("RBL") degranulation test. (Id. at 3:47-4:27.)

The specification could not be clearer here: "Toxicity," in the context of the patents-in-suit, means "the degree to which a substance exhibits negative effects in mouse mortality or RBL degranulation test." See Phillips, 415 F.3d at 1315 (the specification is usually "'dispositive'" and "'the primary basis for construing the claims'") (citations omitted). Because the term is easily "'amenable to construction'" and far from " 'insolubly ambiguous[,]'" the term is not indefinite, as Mylan argues. See Power-One, Inc., 599 F.3d at 1350 (citation omitted). To the extent Sandoz argues "toxicity" should be construed to mean "the property of causing death or adverse reaction," the Court rejects this construction in view of the specification, where Teva provided "a special definition" for "toxicity." See Phillips, 415 F.3d at 1316. In cases such as this, "the inventor's lexicography governs." Id. (citation omitted).

7. "Predetermined" and "Predetermined By Test Reaction"

The terms "predetermined" and "predetermined by a test reaction" appear in several of the claims. Teva argues that both terms should be accorded their ordinary meanings. Defendants, by contrast, argue that the terms should be limited based on the specification and/or the prosecution history.

Claim 1 of the '898 patent, according to Teva, exemplifies how both terms are used in the claims:

What is claimed is:

> 1. A method of manufacturing copolymer-1 of a predetermined molecular weight profile, compromising the steps of:
>
> selecting a predetermined molecular weight profile,
>
> reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having the predetermined molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and
>
> treating said trifluoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperdine solution to form copolymer-1 having the predetermined molecular weight profile.

('898 patent at 5:34-6:11.)

i. "Predetermined"

As Teva emphasizes, of the six times that the term "predetermined" appears, only once does it refer to a predetermination made "by test reaction." (Id. at 6:5-6.) Sandoz nevertheless argues that "by relying on a test reaction" should be read into every instance of the term "predetermined." Sandoz bases its argument on a statement Teva made during the prosecution of the '898 patent. The patent examiner suggested Teva should use the term "predetermined molecular weight profile" rather than "desired molecular weight profile." (See Kramer Decl. Ex. 6 at

p. 2 (Office Action Summary) (Teva v. Sandoz claim construction).) Teva accepted the patent examiner's suggestion, noting, "[i]t is believed that the substitution of 'predetermined' for – desired – clarifies that the molecular weight profile of the product of the claimed method [is] one that is predetermined by a test reaction." (Id. at p. 4 (Amendment Under 37 C.F.R. 1.111).)

While "an applicant can make a binding disavowal of claim scope in the course of prosecuting the patent, [s]uch argument-based disavowals will be found only if they constitute clear and unmistakable surrenders of subject matter." See Cordis Corp. v. Medtronic Ave, Inc., 511 F. 3d 1157, 1177 (Fed. Cir. 2008) (citations omitted). Teva's statement does not "constitute [a] clear and unmistakable surrender[] of subject matter." See id. Mylan, for its part, does not proffer a proposed construction for "predetermined" as a stand-alone term. Accordingly, the Court construes the term "predetermined" to mean "determined beforehand."

ii. "Predetermined by Test Reaction"

As indicated above, claim 1 of the '898 patent refers, on one occasion, to a predetermination made "by test reaction." ('808 patent at 6:5-6.) Sandoz proffers a definition for "test reaction" that mirrors Teva's dispute with Mylan regarding the meaning of "predetermined by test reaction." As a result, the Court considers these terms together.

Although the crux of Defendants' proposed construction is the same—namely, that a test reaction must be performed on the same batch of

protected copolymer-1 used in a later, larger scale reaction—the Court begins by addressing a preliminary matter. Teva and Sandoz agree that the proper construction of the term "protected copolymer-1" is "copolymer-1 containing one or more protecting groups on one or more amino acids." Mylan, however, contends that protected copolymer-1 has a composition that varies from batch-to-batch. In support of this argument, Mylan points to a specification statement indicating that "[p]rotected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971)." ('808 patent at 4:49-50.) According to Mylan, the Teitelbaum copolymerization process necessarily yields batch-to-batch variations. Mylan is wrong. As prior art, Teitelbaum does not define the invention. More importantly, Teitelbaum does not indicate that protected copolymer-1 varies from batch-to-batch. Accordingly, the Court rejects Mylan's proposed construction of protected copolymer-1.[12]

With respect to "test reaction," nothing in the specification indicates that a small-scale test reaction must be performed on the same batch of protected copolymer-1 used in a large-scale test reaction. Example 4 in the specification describes use of a "test reaction" in connection with the chemical method of breaking down the higher molecular weight species of copolymer-1. It provides:

---

[12] In addition, the fact that the specification directs that a test reaction be "performed on every batch" of copolymer-1 ('808 patent at 4:65-67) does not mean, as Mylan argues, that the composition of protected copolymer-1 varies from batch-to-batch.

> Protected copolymer-1 is treated with 33% [hydrobromic acid] in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20 °-28° C. a test reaction is performed on every batch at different time periods for example, from 10-50 hours.
>
> The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7, 000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period [for obtaining molecular weight 7,000±2,000 Da] is 17 hours.

('808 patent at 4:59-5:6.) Based on these directions, if a person of skill in the art wanted to make protected copolymer-1 with an AMW of 7,000±2,000 Da, he or she could follow Example 4 and then rely on the test reaction described in the patent to treat protected copolymer-1 with 33% hydrobromic acid in acetic acid at 26° C for 17 hours. (See id.) Because Example 4 does not indicate the small scale reaction is performed on the same batch of protected copolymer-1 used in the larger scale reaction, according to Dr. Grant, "a person of skill in the art would have understood that the test reactions could be performed on a separate batch and there may not necessarily be a corresponding 'large scale' reaction

for every test reaction." (Grant Decl. ¶ 70 (Teva v. Sandoz claim construction).)

The prosecution history supports this construction. During the prosecution of the '898 patent, for example, Teva explained:

> [O]ne of ordinary skill in the art would recognize that the test reaction is a small-scale version of the method taught in the specification, performed in order to determine the appropriate time and temperature to obtain copolymer-1 having the desired profile. The Examiner has not provided any basis as to why one of ordinary skill in the art would be unable to follow this procedure taught by the present application to make copolymer-1 or trifluoroacetyl copolymer-1 of a desired molecular weight. As noted by the Examiner, pages 8-9 of the specification teach the use of test reactions over a time period and temperature in order to assess the exact parameters which provide copolymer-1 of a particular molecular weight profile; e.g., 17 hours at 26°C to provide copolymer-1 having a molecular weight fraction of 5 to 9 kDa. This assessment allows individuals of ordinary skill in the art to perform larger scale reactions and obtain large volumes of copolymer-1 of a desired molecular weight.

(Blessing Decl. Ex. 2 at TEV000309114-15 (Amendment under 37 C.F.R. 1.111) (Teva v. Sandoz claim construction).) This explanation expressly envisions skilled artisans relying on the test reaction described in the specification to perform larger scale reactions.

For the reasons provided above, the Court construes "predetermined by a test reaction" to mean "determined beforehand by a reaction carried out to determine results of varying reaction conditions."

8. "Multiple Sclerosis"

The parties offer competing constructions for the term "multiple sclerosis." Based on the current record, the Court is unable to construe the term. The Court will hear from the parties regarding the meaning of "multiple sclerosis" at the pre-trial conference scheduled for August 30, 2011 at 1:00 p.m.

CONCLUSION

For the reasons provided above, the disputed claim terms shall have the constructions set forth above. In view of the Court's finding that the claims are capable of construction, Mylan's motion for a summary judgment finding of invalidity on the basis of indefiniteness (Dkt. 96 in 09 Civ. 8824(BSJ)(AJP)) is DENIED. The Clerk of the Court is directed to terminate this motion.

SO ORDERED:

BARBARA S. JONES
UNITED STATES DISTRICT JUDGE

Dated: New York, New York
August 24, 2011

APPENDIX C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD.,

Plaintiffs,

v.

SANDOZ INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTIFCALS, INC.,

Defendants.

Civil Action No. 08-CV-7611 (BSJ) (AJP)

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs,* v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., *Defendants.*	Civil Action No. 09-CV-8824 (BSJ) (AJP)

FINAL JUDGMENT ORDER

This matter having come before the Court upon the Complaint of Plaintiffs Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Inc., Teva Neuroscience, Inc., and Yeda Research and Development Co. (collectively, "Plaintiffs") alleging that Sandoz Inc. and Momenta Pharmaceuticals, Inc. (collectively, the "Sandoz Defendants") infringe U.S. Patent Nos. 7,199,098 ("the '098 patent"), 6,939,539 ("the '539 patent"), 6,054,430 ("the '430 patent"), and 6,620,847 ("the '847 patent") pursuant to 35 U.S.C. §§ 271(a), 271(b), 271(c), and 271(e)(2); Plaintiffs' claims seeking a declaratory judgment of the Sandoz Defendants' patent, the '539 patent, the '430 patent,

and the '847 patent; and the Sandoz Defendants' counterclaims seeking a declaratory judgment of non-infringement, unenforceability, and invalidity of the '098 patent, the '539 patent, the '430 patent, the '847 patent, U.S. Patent No. 5,981,589 ("the '589 patent"), U.S. Patent No. 6,342,476 ("the '476 patent"), U.S. Patent No. 6,362,161 ("the '161 patent"), U.S. Patent No. 5,800,808 ("the '808 patent), and U.S. Patent No. 6,048,898 ("the '898 patent") pursuant to 35 U.S.C. §§ 271(a), 271(b) and 271(c); and upon the Complaint of Plaintiffs alleging that Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (collectively, the "Mylan Defendants") infringe the '098 patent, the '539 patent, the '430 patent, the '847 patent, the '589 patent, the '476 patent, and the '161 patent pursuant to 35 U.S.C. §§ 271(a), 271(b), 271 (c), and 271(e)(2); Plaintiffs' claims seeking a declaratory judgment of the Mylan Defendants* infringement of the '098 patent, '539 patent, the '430 patent, the '847 patent, the '589 patent, the '476 patent, and the '161 patent pursuant to 35 U.S.C. §§ 271(a), 271(b), and 271(c); and the Mylan Defendants' counterclaims seeking a declaratory judgment of non-infringement, unenforceability, and invalidity of the '098 patent, the '539 patent, the '430 patent, the '847 patent, the '589 patent, the '476 patent, the '161 patent, the '808 patent, and the '898 patent pursuant to 35 U.S.C. §§ 271(a), 271(b) and 271(c),

IT IS on this 23rd day of July,

1. ORDERED AND ADJUDGED for the reasons set forth in the Court's Opinion dated June 22, 2012, that FINAL JUDGMENT IS ENTERED IN FAVOR

OF PLAINTIFFS and AGAINST THE SANDOZ DEFENDANTS with respect to Plaintiffs' claims that the product which is the subject of the Sandoz Defendants' ANDA No, 90-218 infringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1 and 2 of the '430 patent, and claims 1 and 6 of the '847 patent pursuant to 35 U.S.C. § 271(e)(2)(A), and that each of these asserted claims against the Sandoz Defendants is valid, enforceable, and infringed;

2. IT IS FURTHER ORDERED AND, ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE SANDOZ DEFENDANTS with respect to Plaintiffs' declaratory judgment claims pursuant to 35 U.S.C. §§ 2201,2202, that the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 if commercially manufactured, used, marketed, sold, or offered for sale within the United States or imported thereto would infringe claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1 and 2 of the '430 patent, claims 1 and 6 of the '847 patent against the Sandoz Defendants pursuant to 35 U.S.C. §§ 271(a), (b), and (c), and IT IS DECLARED that each of these asserted claims against the Sandoz Defendants is valid, enforceable, and infringed;

3. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE SANDOZ DEFENDANTS with respect to the Sandoz Defendants' counterclaims

seeking declaratory judgment of non-infringement, invalidity and unenforceability of claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1 and 2 of the '430 patent, claims 1 and 6 of the '847 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claim 1 of the '808 patent, and claims 1 and 2 of the '898 patent, all such counterclaims are DISMISSED WITH PREJUDICE, and IT IS DECLARED that each of these asserted claims against the Sandoz Defendants is valid, enforceable, and infringed by the product which is the subject of the Sandoz Defendants' ANDA No. 90-218;

4. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE MYLAN DEFENDANTS with respect to Plaintiffs' claims that the product which is the subject of the Mylan Defendants' ANDA No, 91-646 infringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1, 2, and 3 of the '430 patent, claims 1 and 6 of the '847 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent pursuant to 35 U.S.C. §271 (e)(2)(A), and that each of these asserted claims against the Mylan Defendants is valid, enforceable, and infringed;

5. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE MYLAN DEFENDANTS with respect to Plaintiffs' declaratory judgment claims pursuant to pursuant to 35 U.S.C. §§ 2201,2202, that

the product which is the subject of the Mylan Defendants' ANDA No. 91-646 if commercially manufactured, used, marketed, sold, or offered for sale within the United States or imported thereto would infringe claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1, 2, and 3 of the '430 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1 and 6 of the '847 patent against the Mylan Defendants pursuant to 35 U.S.C. §§ 271(a), (b), (c), and IT IS DECLARED that each of these asserted claims against the Mylan Defendants is valid, enforceable, and infringed;

6. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE MYLAN DEFENDANTS with respect to the Mylan Defendants' counterclaims seeking declaratory judgment of non-infringement, invalidity, and unenforceability of claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1,2, and 3 of the '430 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claim 1 of the '808 patent, claims 1 and 6 of the '847 patent, and claims 1, 2, and 3 of the '898 patent, all such counterclaims are DISMISSED WITH PREJUDICE, and IT IS DECLARED that each of these asserted claims against the Mylan Defendants is valid, enforceable, and infringed by the product which is the subject of the Mylan Defendants' ANDA No. 91-646;

7. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any

approval by the U.S. Food and Drug Administration ("FDA") of the Sandoz Defendants' ANDA No. 90-218 shall not be earlier than the expiration of the '098 patent, the '539 patent, the '589 patent, the '476 patent, the '161 patent, the '430 patent, and the '847 patent on May 24, 2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable, the date any such exclusivity ends, but that Plaintiffs will provide written notice to the Sandoz Defendants of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA;

8. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271 (e)(4)(A), the effective date of any approval by the FDA of the Mylan Defendants' ANDA No. 91-646, shall not be earlier than the expiration of the '098 patent, the '539 patent, the '589 patent, the '476 patent, the '161 patent, the '430 patent, and the '847 patent on May 24, 2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable, the date any such exclusivity ends, but that Plaintiffs will provide written notice to the Mylan Defendants of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA;

9. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(B), the Sandoz Defendants and each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States,

of the product which is the subject of the Sandoz Defendants' ANDA No. 90-218, which infringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1 and 2 of the '430 patent, and claims 1 and 6 of the '847 patent until May 24, 2014;

10. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(B), the Mylan Defendants, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of the Mylan Defendants' ANDA No. 91-646, which infringes claims 1 and 8 of the '098 patent claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1, 2, and 3 of the '430 patent, and claims 1 and 6 of the '847 patent until May 24, 2014;

11. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 283, the Sandoz Defendants, their respective officers, directors, employees, agents, successors, affiliates and assigns, and all persons and entities acting in concert or participation with them are permanently enjoined from directly or indirectly engaging in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 until the

expiration of the '808 patent on September 1, 2015, and are permanently enjoined from directly or indirectly engaging in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 until the expiration of the '098 patent, the '539 patent, the '430 patent, the '589 patent, the '476 patent, the '161 patent, the '847 patent, and the patent '898 patent on May 24, 2014;

12. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 283, the Mylan Defendants, their respective officers, directors, employees, agents, successors, affiliates and assigns, and all persons and entities acting in concert or participation with them are permanently enjoined from directly or indirectly engaging in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Mylan Defendants' ANDA No. 91-646 until the expiration of the '808 patent on September 1, 2015, and are permanently enjoined from directly or indirectly engaging in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Mylan Defendants' ANDA No. 91-646 until the expiration of the '098 patent, the '539 patent, the '430 patent, the '589 patent, the '476 patent, the '161 patent, the '847 patent, and the patent '898 patent on May 24, 2014;

13. IT IS FURTHER ORDERED THAT nothing in this FINAL JUDGMENT ORDER shall be construed to limit the rights of the parties pursuant to 35 U.S.C. § 271(e)(1);

14. IT IS FURTHER ORDERED that the Sandoz Defendants and the Mylan Defendants do not waive any rights to appeal any portion of this final judgment including the injunctive relief granted, to the extent the Court's findings or holdings are modified on appeal; and

15. IT IS FURTHER ORDERED that any request for costs pursuant to Fed. R. Civ. P 54(d)(1) and Local Civil Rule 54.1 shall be filed within forty-five (45) days of entry of this FINAL JUDGMENT ORDER, and any motion for attorneys' fees pursuant to Fed. R. Civ. P 54(d)(2) and 35 U.S.C. § 285 shall be filed within forty-five (45) days of entry of this FINAL JUDGMENT ORDER. The Sandoz Defendants' and the Mylan Defendants' opposition to any request for costs pursuant to Fed. R. Civ. P 54(d)(1) and Local Civil Rule 54,1 shall be filed within ninety (90) days of the filing of such request, and the Sandoz Defendants' and the Mylan Defendants' opposition to any motion for attorneys' fees pursuant to Fed. R. Civ. P 54(d)(2) and 35 U.S.C. § 285 shall be filed within ninety (90) days of the filing of such motion. Plaintiffs' reply in support of any motion for attorneys' fees shall be filed within thirty (30) days of the filing of opposition by the Sandoz or Mylan Defendants.

_____

Hon. Barbara S. Jones
U.S. District Judge

APPENDIX D

Note: This order is nonprecedential

United States Court of Appeals for the Federal Circuit

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA NEUROSCIENCE, INC., AND YEDA RESEARCH AND DEVELOPMENT CO., LTD.,
Plaintiffs-Appellants,

v.

SANDOZ, INC., AND MOMENTA PHARMACEUTICALS INC.,
Defendants-Appellants,

AND

MYLAN PHARMACEUTICALS INC., MYLAN INC., AND NATCO PHARMA LTD.,
Defendants-Appellants,

AND

SANDOZ INTERNATIONAL GMBH, AND NOVARTIS AG,
Defendants.

2012-1567, 1568, -1569, -1570

Appeals from the United States District Court for the Southern District of New York in consolidated Nos. 08-CV-7611 and 09-CV-8824, Judge Barbara S. Jones.

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before Rader, *Chief Judge*, Newman, Lourie, Dyk, Prost, Moore, O'Malley, Reyna, Wallach, Taranto, Chen, *Circuit Judges*, and Benson, *District Judge*.*

PER CURIAM

O R D E R

A combined petition for panel rehearing and for rehearing en banc having been filed by the Appellees, and the petition for rehearing, having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is,

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

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* Honorable Dee V. Benson, District Judge, United States Court for the District of Utah, sitting by designation.

The mandate of the court will issue on October 25, 2013.

Circuit Judge Hughes did not participate.

FOR THE COURT

October 18, 2013
Date

/s/ Daniel E. O'Toole
Daniel E. O'Toole
Clerk

APPENDIX E

Note: This order is nonprecedential

United States Court of Appeals for the Federal Circuit

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA NEUROSCIENCE, INC., AND YEDA RESEARCH AND DEVELOPMENT CO., LTD.,
Plaintiffs-Appellants,

v.

SANDOZ, INC., AND MOMENTA PHARMACEUTICALS INC.,
Defendants-Appellants,

AND

MYLAN PHARMACEUTICALS INC., MYLAN INC., AND NATCO PHARMA LTD.,
Defendants-Appellants,

AND

SANDOZ INTERNATIONAL GMBH, AND NOVARTIS AG,
Defendants.

2012-1567, 1568, 1569, -1570

Appeals from the United States District Court for the Southern District of New York in consolidated Nos. 08-CV-7611 and 09-CV-8824, Judge Barbara S. Jones.

ON MOTION

Before Rader, *Chief Judge*, Moore, *Circuit Judge*, and Benson, *District Judge*.*

PER CURIAM

O R D E R

Appellees Teva Pharmaceuticals USA, Inc., et al. separately move to correct the judgment in this case and to stay the issuance of the mandate pursuant to Fed. R. App. P. 41(d)(2).

Upon consideration thereof,

IT IS ORDERED THAT:

The motions are denied.

FOR THE COURT

November 1, 2013
Date

/s/ Daniel E. O'Toole
Daniel E. O'Toole
Clerk

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* Honorable Dee V. Benson, District Judge, United States Court for the District of Utah, sitting by designation.

APPENDIX F

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs,* v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., *Defendants.*	Civil Action No. 09-CV-8824 (BSAJ) (AJP)

DECLARATION OF GREGORY A. GRANT, PH.D.

1. I have been retained by counsel for Teva Pharmaceuticals USA, Inc., Teva Pharmaceuticals Industries Ltd., Teva Neuroscience, Inc., (collectively, "Teva") and Yeda Research and Development Co. (collectively, "Plaintiffs") to provide my opinions as an expert witness regarding U.S. Patents Nos. 5,800,808 ("the '808 patent"), 5,981,589

("the '589 patent"), 6,048,898 ("the '898 patent"), 6,054,430 ("the '430 patent"), 6,342,476 ("the '476 patent"), 6,362,161 ("the '161 patent"), 6,620,847 ("the '847 patent"), 6,939,539 ("the '539 patent"), and 7,199,098 ("the '098 patent") (collectively, "the patents-in-suit," Exhibit B).

2. I am a professor of Biochemistry in Medicine and of Developmental Biology at the School of Medicine at Washington University in St. Louis, Missouri. I have over 30 years of experience teaching and directing research related to protein and synthetic polypeptide characterization. My own research is focused primarily on the investigation of the regulatory processes of proteins.

3. I have also directed the Protein and Nucleic Acid Chemistry Laboratory (PNACL), an instrumentation core laboratory at Washington University, for over 25 years. In that regard, my staff and I have provided sophisticated analytical and synthetic research capabilities to researchers in the field of protein and synthetic polypeptide chemistry.

4. I have been using size exclusion chromatography ("SEC") and related technologies for over 35 years. I have used this technique to measure the molecular weights of proteins.

5. A copy of my curriculum vitae is attached hereto as Exhibit A, and a short summary follows in section I below.

I. MY BACKGROUND

6. I received a Bachelor of Science in Biochemistry from Iowa State University in 1971. I received a Ph.D. in Biochemistry from University of Wisconsin, Madison in 1975, and conducted three years of postdoctoral research at Washington University School of Medicine.

7. In addition to my academic positions, I have served on several editorial boards for various scientific journals and book series. I have also served on numerous advisory committees and have actively participated in the National Institute of Health, Biochemistry Study Section. In that regard, I have been invited to review federal and state research grant applications and to review academic papers for journal and/or conference publication in the field of biochemistry, protein chemistry, polypeptide science, and biomolecular techniques.

8. I have been invited to present numerous scientific lectures and seminars at conferences, companies, and universities. These lectures and seminars have focused on various aspects of protein analysis, including the instrumentation and techniques for the characterization of proteins and synthetic polypeptides.

9. My research has contributed to the authorship of over 100 peer-reviewed publications and many invited articles/chapters in books, encyclopedias, and scientific journals. Examples of book contributions include chapters in Current Protocols in Protein Science and in Synthetic Peptides: A User's Guide and entries of synthetic peptides in Encyclopedia of Molecular Biology and Molecular Medicine and in

Molecular Biology and Biotechnology: A Comprehensive Desk Reference.

II. FEES

10. My fees for services as an expert witness in this litigation are $500 per hour plus expenses and $750 per hour for deposition and trial testimony. My compensation is not dependent in any way upon the opinions formed or the outcome of this litigation.

III. PRIOR EXPERT TESTIMONY

11. In the last five years (from 2004-2009), I have testified at three depositions in the case of *Teva Pharmaceuticals USA v. Sandoz Inc.*, No. 08-cv-7611 (BSJ)(AJP) (S.D.N.Y.).

IV. MATERIALS CONSIDERED

12. My opinions are based on the patents-in-suit and their prosecution histories[1], the materials identified in the Declaration, my knowledge, education, and experience, and the materials listed in Exhibit C.

V. SUMMARY OF EXPECTED TESTIMONY

13. I have been informed that the Plaintiffs filed the present lawsuit against Mylan Pharmaceuticals Inc., Mylan Inc. and Natco Pharma Ltd. (collectively,

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[1] I understand that the correspondence between the patent applicants and the United States Patent and Trademark office ("the Patent Office") leading to the issuance of the patent is called the prosecution history of that patent.

"Defendants") on the basis that Defendants infringe the claims of the patents-in-suit.

14. If called as a witness, I expect to testify on the following topics and to provide opinions and testimony on what is summarized in this Declaration:

a. The state of the art at times relevant to the subject matter set forth below;

b. The level of ordinary skill in the art to which the patents-in-suit are directed;

c. The patents-in-suit, their specification and claims, the science underlying what is disclosed in the patents-in-suit, the interpretation of the claims of the patents-in-suit by the person of ordinary skill in the art to which the patents-in-suit are directed; and

d. My opinions about how certain terms and phrases in the claims of the patents-in-suit should be interpreted by a person of ordinary skill in the art.

VI. THE PATENTS-IN-SUIT

15. The patents-in-suit, all of which are entitled "Copolymer-1 Improvements in Compositions of Copolymers," generally relate to low molecular weight copolymer-1 and methods of making low molecular weight copolymer-1. The patents-in-suit have essentially the same specification ("the specification"), but have different claims.

16. Copolymer-1 was developed by three of the inventors of the patents-in-suit (Michael Sela, Dvora Teitelbaum, and Ruth Arnon) and their co-workers many years prior to the filing of the applications for the patents-in-suit. The prior art copolymer-1 is described in the patents-in-suit as having average molecular weights of 23,000 daltons (e.g., the '808 patent, col. 1, lines 34-37). The patents describe copolymer-1 of lower molecular weight than the original copolymer-1. In addition, the patents describe methods of making copolymer-1 of lower molecular weight (e.g., patents-in-suit, Examples 1, 3, and 4) and the use of lower molecular weight copolymer-1 to treat multiple sclerosis (e.g., the '808 patent, col. 1, lines 51-53 and col. 2, lines 47-48).

17. The patents describe the characteristics of low molecular weight copolymer-1, which include, for example, the average molecular weight of the copolymer-1 and the percentage of the species within a certain molecular weight range (e.g., the '808 patent, col. 1, line 64-col. 2, line 14). In Example 1, the patents describe that the molecular weight distribution of copolymer-1 was determined on a calibrated gel filtration column. The molecular weight distributions of copolymer-1 batches are illustrated in Figures 1 and 2.

VII. LEVEL OF ORDINARY SKILL IN THE ART

18. I understand that patent claims are to be interpreted from the point of view of a person of ordinary skill in the relevant art in view of the description of the invention in the patent.

19. I have reviewed the specifications, claims, and relevant portions of the prosecution histories of the patents-in-suit.

20. I understand that the relevant time period for the person of ordinary skill in the art to interpret the claim terms is the filing date of the patent. I also understand that each of the patents-in-suit, although filed on different dates, claim priority to a continuation-in-part application filed May 22, 1995, which in turn claims priority to applications filed November 23, 1994 and May 24, 1994.

21. Based on my experience, it is my opinion that a person of ordinary skill in the art of the patents-in-suit would have had an advanced degree or equivalent in a chemical or biological discipline, and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides. In my experience, this person of skill in the art would also have had access to and the ability to consult with other scientists having related and/or complementary knowledge and experience in the areas of polymer chemistry, biochemistry, analytical chemistry, separation technology, medicine, and toxicology.

VIII. BACKGROUND POLYPEPTIDE AND MOLECULAR WEIGHT PRIMER

A. MOLECULE, MOLECULAR WEIGHT, AND MOLAR FRACTION

22. An atom is the smallest unit of a chemical element, having all the characteristics of that element. The mass of an atom is often expressed

using a unit called dalton (Da). A dalton is defined as 1/12 of the mass of a carbon-12 atom, where its mass is set equal to exactly 12 mass units. Each atom of a chemical element has a unique atomic weight.[2] For example, the most common form of the hydrogen atom has an atomic weight of 1, of carbon, 12, of nitrogen, 14, and of oxygen, 16.[3]

23. A molecule is the smallest unit of a chemical substance that still displays the properties associated with that substance. Molecules may contain two atoms of the same element, such as oxygen (O_2), which has two oxygen atoms, or they may consist of two or more different atoms, such as water (H_2O), which has two hydrogen atoms and one oxygen atom.

24. The molecular weight of a molecule is calculated by adding the atomic weights of the atoms in the molecule. For example, the molecular weight of a water (H_2O) molecule is calculated by adding the atomic weights of two hydrogen atoms and one oxygen atom (1+1+16=18).

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[2] Although relative atomic and molecular weights are dimensionless quantities, in my experience, these quantities are often referred to as having a mass in daltons, e.g., an atomic weight or a molecular weight of x daltons.

[3] The atoms of an element may exhibit different atomic weights. Atoms of the same element which differ in atomic weight are called isotopes. For example, carbon can exist as isotopes having atomic weights of 12 (most common), 13 (far less common), or 14 (even less common). For the remainder of this report, when referring to the atomic weight of an element, I will make reference to the most common form of that element.

25. A mole is defined as the quantity of a substance that has the same number of molecules as found in 12 grams of carbon-12. One mole of a substance always contains 6.022×10^{23} molecules, which has a weight in grams that equals the molecular weight of that substance. For example, water has a molecular weight of 18, the mass of a water molecule is 18 daltons, and therefore one mole of water has a weight of 18 grams.[4]

26. In expressing the composition of a mixture, molar fraction refers to the number of moles of a particular component in the mixture divided by the total number of moles of all components in the mixture. Because the number of molecules in one mole of any substance is always 6.022x1023, molar fraction is also equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Similarly, molar ratio refers to the ratio of the number of moles of each component in a mixture, which is equivalent to the ratio of the number of molecules of each component in a mixture.

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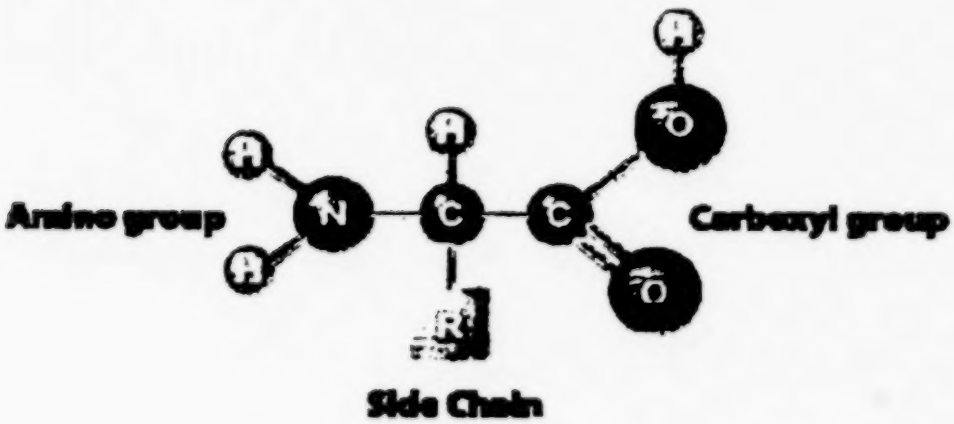
[4] In my experience, the terms "weight" and "mass" are used interchangeably.

B. AMINO ACIDS AND POLYPEPTIDES

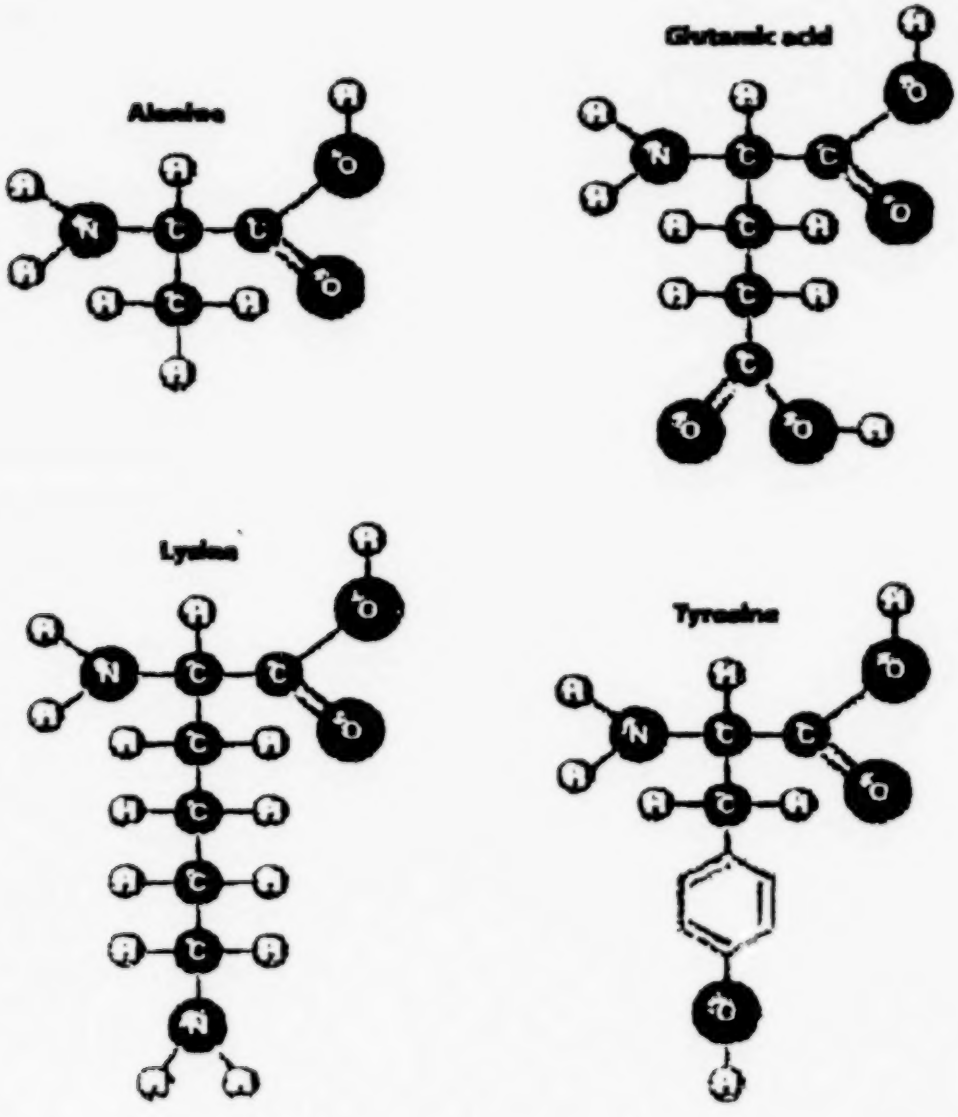
27. Amino acids are the basic building blocks of proteins. Each amino acid molecule contains: (1) an amino group, NH_2; (2) a carboxylic acid (carboxyl) group, COOH, and; (3) another chemical group referred to as a side chain represented by R in the formula shown in Figure A below.

Figure A. Amino Acid



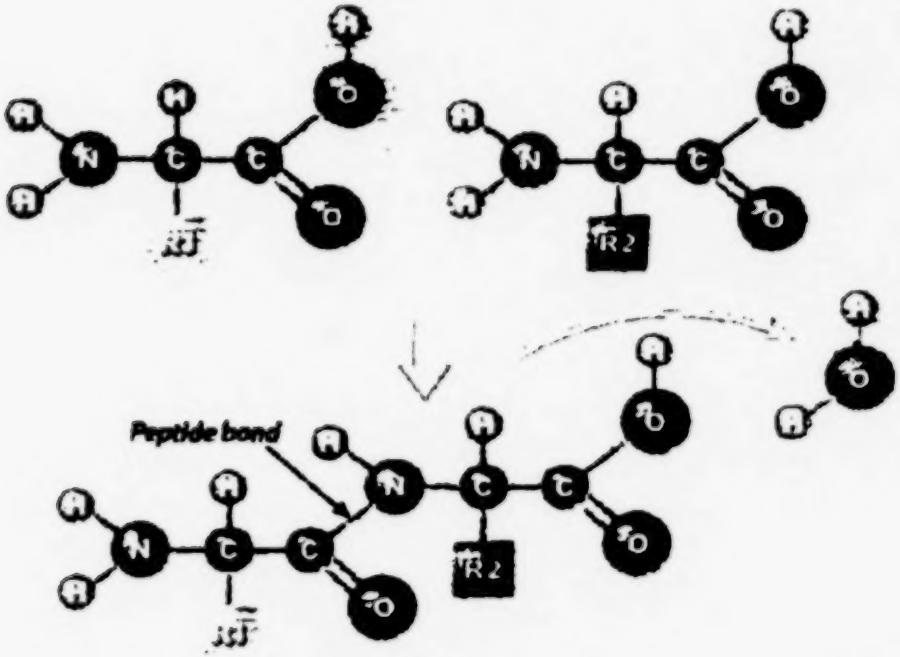
28. There are twenty different genetically-coded amino acids that make up proteins in mammals, each with a different R-group. For example, the simplest amino acid is glycine, with the R-group being a hydrogen atom. The R-groups of alanine, glutamic acid, lysine, and tyrosine are shown in the formulas in Figure B below.

Figure B. Alanine, Glutamic acid, Lysine, and Tyrosine



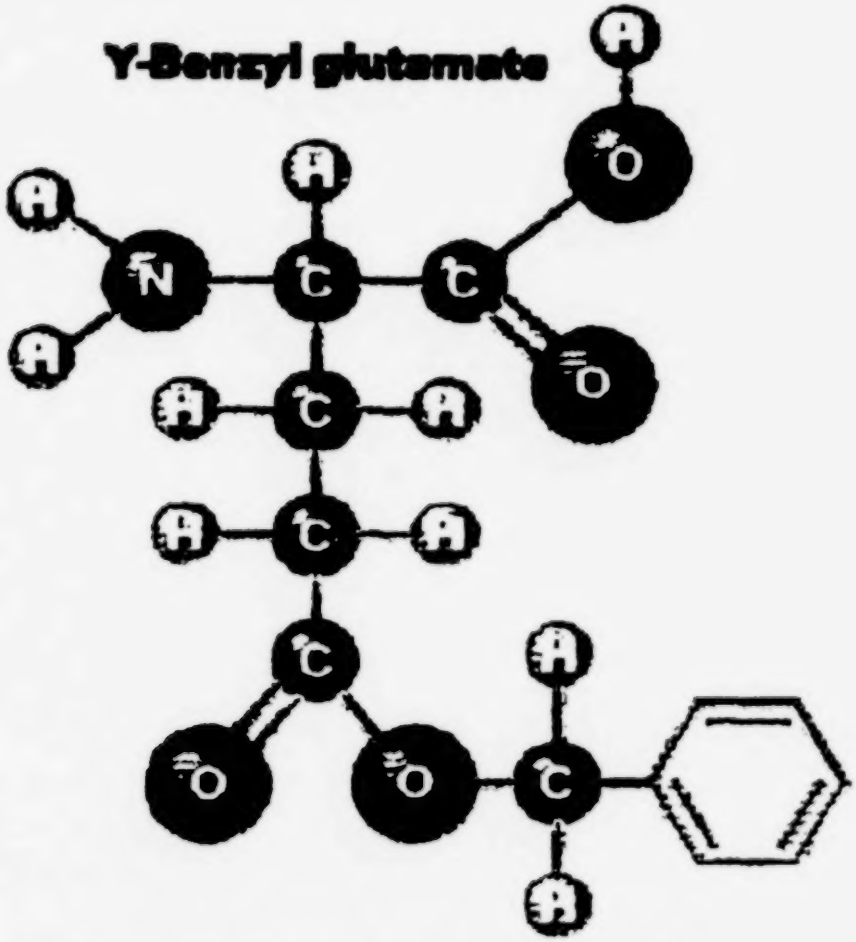
A peptide bond is a linkage between two amino acids that is formed when the amino group of one amino acid reacts with the carboxyl group of another amino acid. Polypeptides are chains of amino acids held together by peptide bonds. Generally, peptide bonds form as shown in Figure C below.

Figure C. Formation of a peptide bond



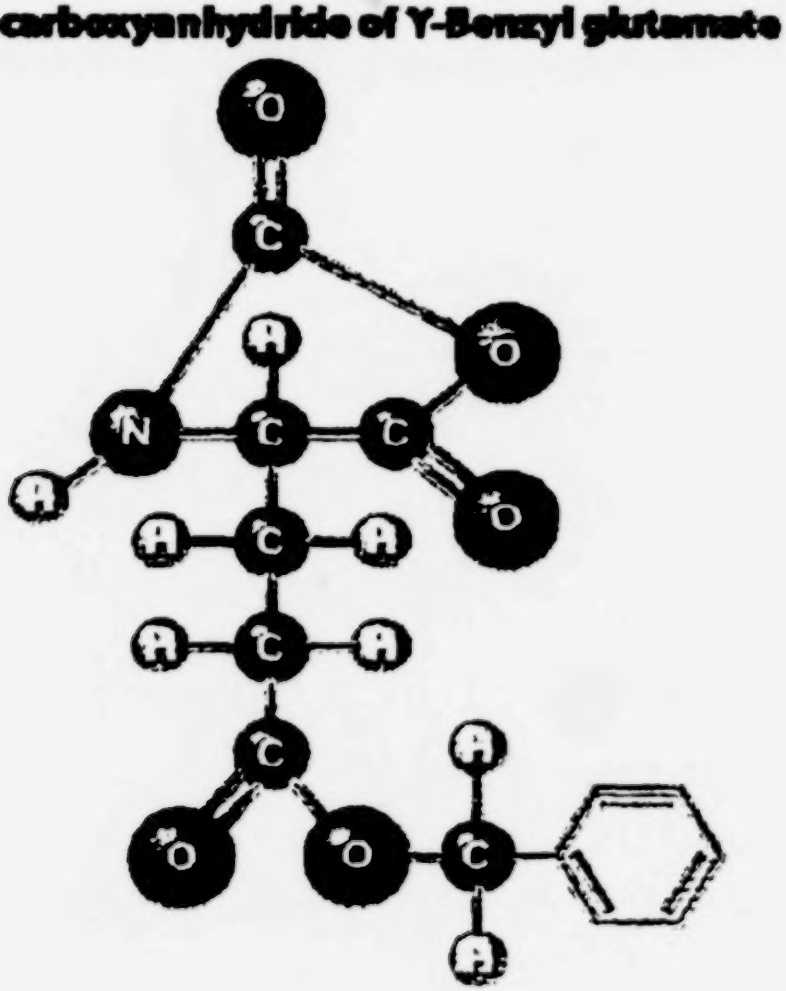
29 In some cases, the R-groups of some amino acids contain chemical groups that are potentially reactive, such as amino or carboxyl groups. Therefore, to avoid unwanted reactions during chemical synthesis, these potentially reactive chemical groups need to be modified in such a way that they do not interfere with peptide bond formation. Typically, the protection of a potentially reactive chemical group is achieved by chemically modifying it so that it is no longer reactive. The process of chemical modification is sometimes called "protecting" and the chemical modification is called a "protecting group" After the polypeptides are formed, these protecting groups can be removed. For example, a protected glutamic acid is shown in Figure D below.

Figure D. Protected glutamic acid



30. As amino acids themselves generally have low reactivity, in protein biosynthesis the reactions between amino acids are facilitated by enzymes. To facilitate the chemical synthesis of polypeptides, amino acids are converted into a more "reactive" form first. One example of a reactive form of an amino acid is the formation of a carboxyanhydride that links the α-amino and the α-carboxyl groups, forming an N-carboxyanhydride, or NCA, of the corresponding amino acid. For example, the NCA of a protected glutamic acid is shown in Figure E below.

Figure E. NCA of protected glutamic acid

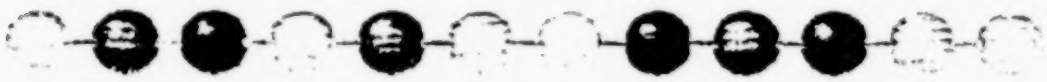


31. When these amino acid NCAs are mixed together, they can be activated by an initiator, and this will cause them to react with each other to form polypeptides. A commonly used initiator for this reaction is an amine such as diethylamine.

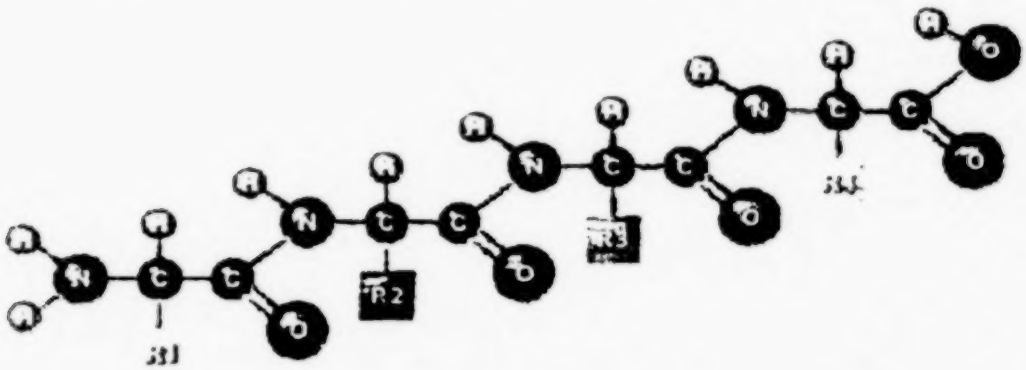
C. COPOLYMER-1

32. A polymer molecule is a molecule composed of monomers[5].

A copolymer is a polymer composed of more than one type of monomer.



For example, a polypeptide made of more than one type of amino acid monomer is a copolymer.



33. When several different monomers are allowed to react with each other to form a polymer or copolymer, they can react in any order and to a greater or lesser extent. Such polymerization reactions therefore often result in molecules comprised of various numbers of monomers (and hence various sizes).

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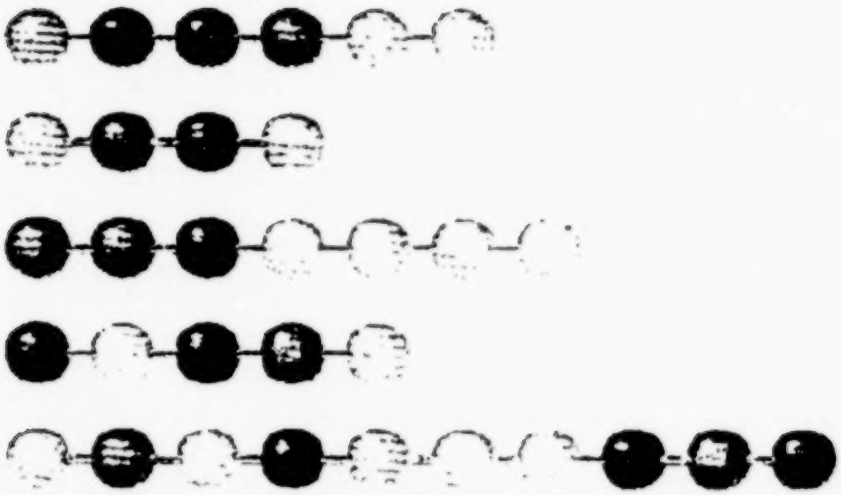
[5] An amino acid, for example, is a monomer.



Therefore, the terms "polymer" and "copolymer" are often used to refer to a collection of molecules with non-uniform sizes, and non-uniform orders of monomers.[6]

34. Copolymer-1 is a name given by its developers to a specific kind of copolymer made of four amino acids, namely alanine, glutamic acid, lysine, and tyrosine. The original copolymer-1 was synthesized by the method described in U.S. Patent No. 3,849,550 ("the '550 patent," attached as Exhibit D) and Teitelbaum *et al.*, Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide, *Eur. J. Immunol.*, 1971. 1:242-248 ("Teitelbaum," attached as Exhibit E). The method described in the prior art involves:

i. Polymerization to make protected copolymer-1: polymerizing the NCAs of alanine, γ-benzyl-protected glutamic acid,

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[6] The order of monomers in a polymer is sometimes referred to as the "sequence", especially when such monomers are amino acids.

and trifluoroacetyl-protected lysine, and tyrosine, in a molar ratio of about 5:2:4:1[7], at room temperature in anhydrous dioxane with diethylamine as the initiator (see Exhibit E, Teitelbaum, p. 243, § 2.3.1);

ii. Debenzylation to make trifluoroacetyl copolymer-1: removing the *y*-benzyl protecting groups on the glutamic acid residues by treating the protected copolymer-1 from step i with hydrogen bromide in glacial acetic acid (see Exhibit E, Teitelbaum, p. 243, § 2.3.1); and

iii. Making copolymer-1: removing the trifluoroacetyl protecting groups on the lysine residues by treating the trifluoroacetyl copolymer-1 with 1M piperidine (see Exhibit E, Teitelbaum, p. 243, § 2.3.1).

The alanine, glutamic acid, lysine, and tyrosine in the resulting copolymer-1 have a molar ratio of about 6:2:5:1 (see Exhibit E, Teitelbaum, p. 243, Table 1). Teitelbaum describes the resulting copolymer-1 as having a molecular weight of 23,000 (see Exhibit E, Teitelbaum, p. 242, Abstract).

35. The patents-in-suit describe that copolymer-1 of lower molecular weight can be obtained by either removing undesired high molecular weight species or using a different reaction time and/or temperature that had been described for the debenzylation step (e.g., the '808 patent, col. 2, lines 29-40). As described

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[7] See Exhibit E, Teitelbaum, p. 243, Table 1.

in the patents-in-suit, such lower molecular weight copolymer-1 showed lower negative effects in a mouse mortality and/or an RBL degranulation test. See Example 2 of the patents-in-suit.

D. MOLECULAR WEIGHT OF POLYMERS

36. Because a polymer composition often includes molecules of varying weights, the molecular weight of such a polymer cannot be characterized by the molecular weight of any single species. The most precise way of describing the molecular weight of such a polymer is a complete molecular weight distribution, i.e., knowledge of the mole or weight fraction of each species. See Flory, Principles of Polymer Chemistry, 1953, p. 317 (attached as Exhibit F). However, for purposes of simplicity and practicality, the molecular weight of a polymer is often expressed in a single, average molecular weight.

37. There are many ways to analyze the molecular weight of a polymer. The molecular weight of a polymer can be measured using methods such as osmometry, light scattering (also known as "MALLS[8]"), ultracentrifugation, and mass spectrometry, such as MALDI[9] Alternatively, the polymer can be separated into fractions, each with a narrow size distribution, using methods such as size exclusion chromatography ("SEC", also known as gel permeation chromatography ("GPC") or gel filtration chromatography). Thereafter, the molecular weight

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[8] Multi-Angle Laser Light Scattering

[9] Matrix-Assisted Laser Desorption Ionization

of each fraction is measured directly using the methods referred to above, or measured indirectly by comparing them to polymer standards for which molecular weights have previously been determined.

38. Depending on the methods used, the molecular weight obtained may represent different types of average molecular weight. For example, when a sample of a polymer is measured by osmometry, the molecular weight obtained is a number average molecular weight (commonly referred to as "M_n"), which represents the total weight of the sample divided by the total number of moles of molecules which it contains. On the other hand, when a sample of a polymer is measured by MALLS, the larger molecules will make a greater contribution to the light scattering than an equal weight of smaller ones, and the molecular weight obtained is a weight average molecular weight (commonly referred to as "M_w"). In a sample containing non-uniform molecular species, M_w is always larger than M_n because the larger molecules are "weighted" more heavily in the weight averaging.

39. When a sample of a polymer is analyzed by size exclusion chromatography, a molecular weight distribution will be obtained, and the molecular weight at the highest point of the resulting chromatogram[10] is referred to as the peak molecular weight, or peak average molecular weight (commonly referred to as "M_p"). The values for M_n and M_w can be further calculated using the size exclusion chromatography data. Unlike M_n and M_w, M_p does

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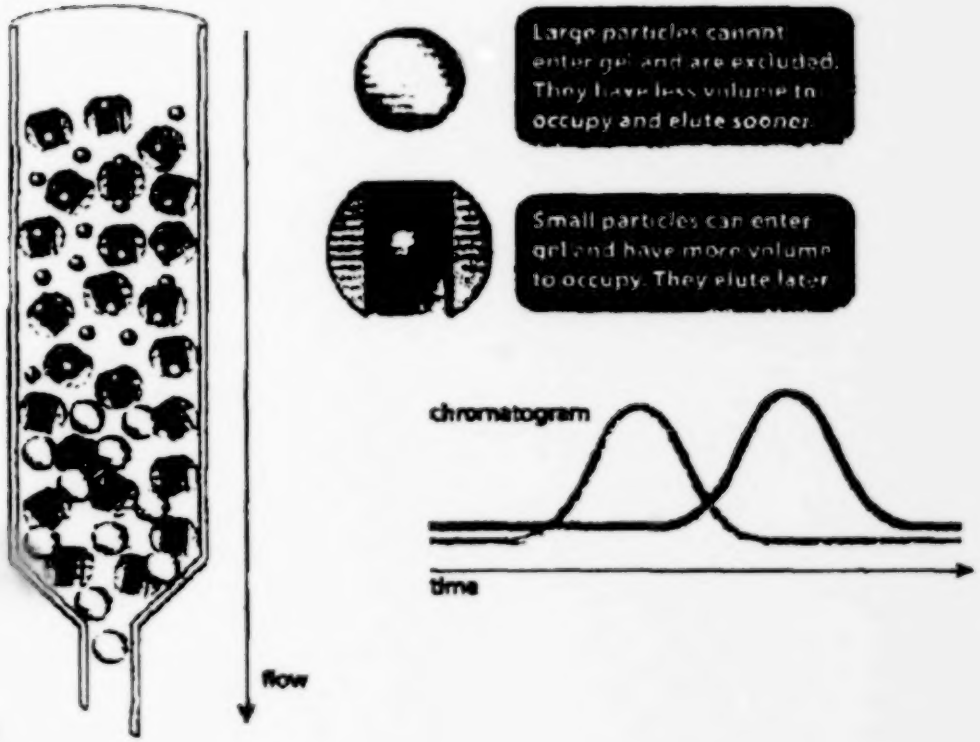
[10] A chromatogram is the visual output of the size exclusion chromatography procedure.

not require additional calculation and can be read directly from a chromatogram in combination with a calibration curve.

E. SIZE EXCLUSION CHROMATOGRAPHY (SEC)

40. The patents describe the use of a calibrated gel filtration column to determine the molecular weight distribution of copolymer-1. See Example 1 of the patents-in-suit. SEC was well understood at the time the patent applications were filed in 1994. Typically, SEC is performed by passing a solution of a polymer down a column packed with a porous gel, which separates the polymer into fractions based on its hydrodynamic properties, which are commonly equated to molecular size. The gel particles in the column contain pores of a predetermined size range. Smaller molecules more easily diffuse into these pores and therefore are retarded to a greater extent than larger molecules. Larger molecules bypass the small pores and come out of the column earlier (having lower elution volume). The elution volume, or retention time at constant flow rate, is directly related to the hydrodynamic size of the molecules, which is in turn related to molecular weight. The concept of SEC is illustrated using two different uniform-sized molecules in Figure F below.

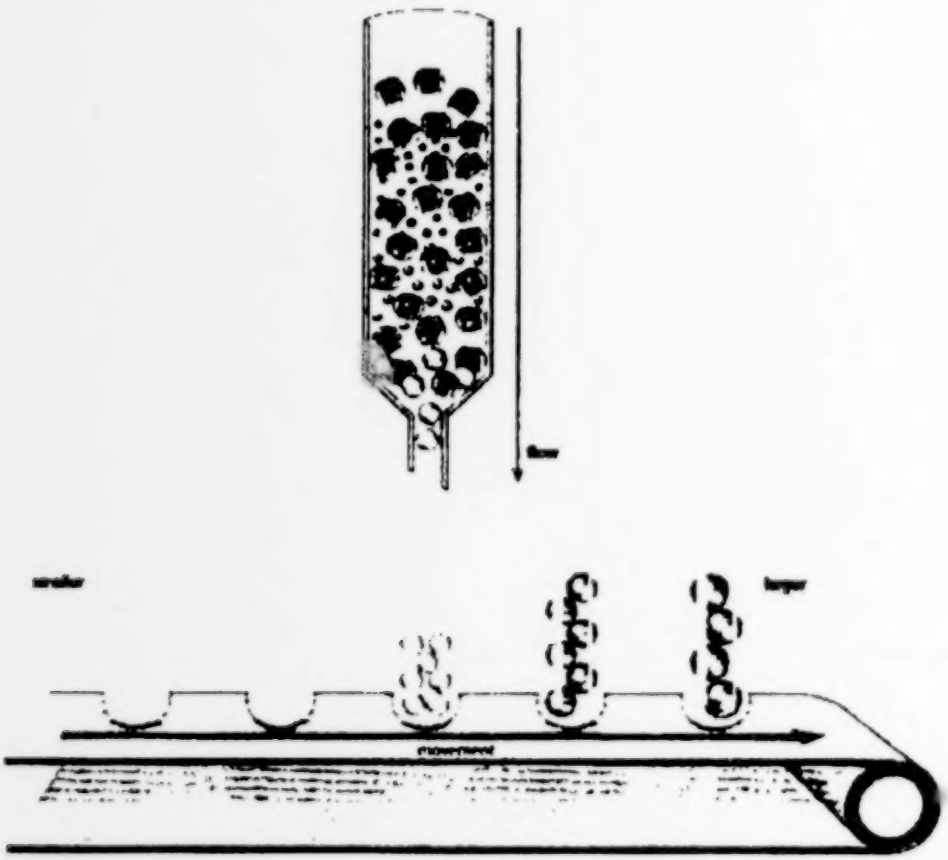
Figure F. Size Exclusion Chromatography



41. Thus, through SEC, the polymer molecules are separated into multiple fractions, each including molecules of a certain size that come out at a certain elution volume, as shown in Figure G below.[11]

[11] Each fraction includes molecules that come out in a discrete volume range. For practical purposes, the molecules within reach fraction are treated as if they have the same size.

Figure G. Separating molecules using SEC

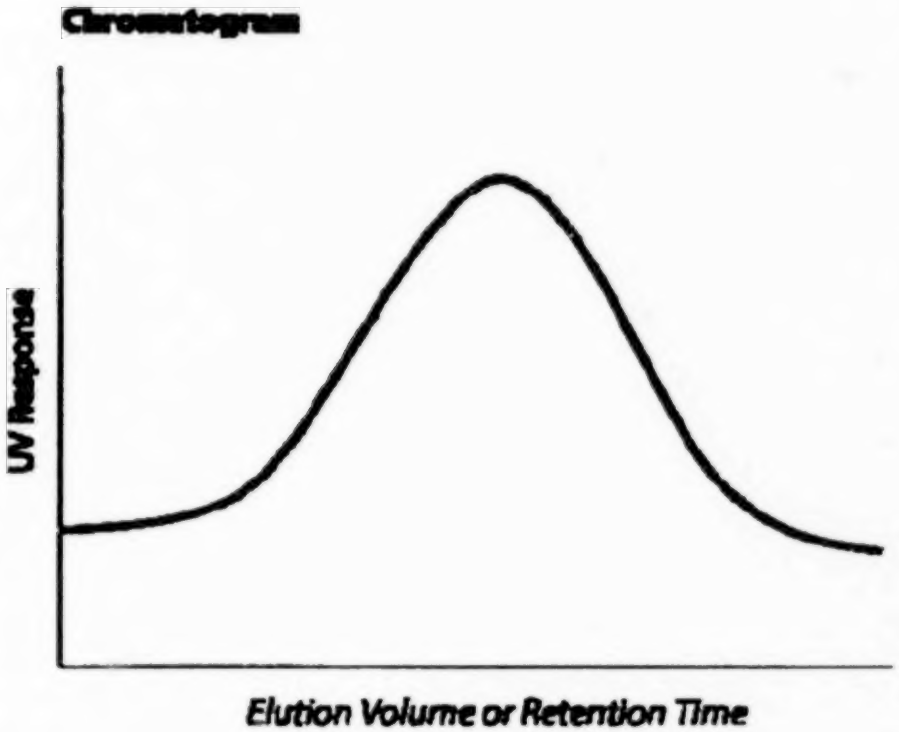


The total amount of the molecules within each fraction can be determined through the measurement of an optical response such as ultraviolet ("UV") absorbance.[12] A chromatogram is generated by plotting UV absorbance versus elution volume or retention time. The peak on the chromatogram corresponds to a fraction that contains the largest amount of polymer, the

[12] For example, UV absorption at 275 nm detects the amount of tyrosine in a fraction. Assuming that the overall ratio of tyrosine in the polypeptides is constant, the UV absorption is proportional to the amount of all polypeptides in that fraction.

molecular weight of which is the peak or "peak average" molecular weight. A typical chromatogram of a polymer is shown in Figure H below.

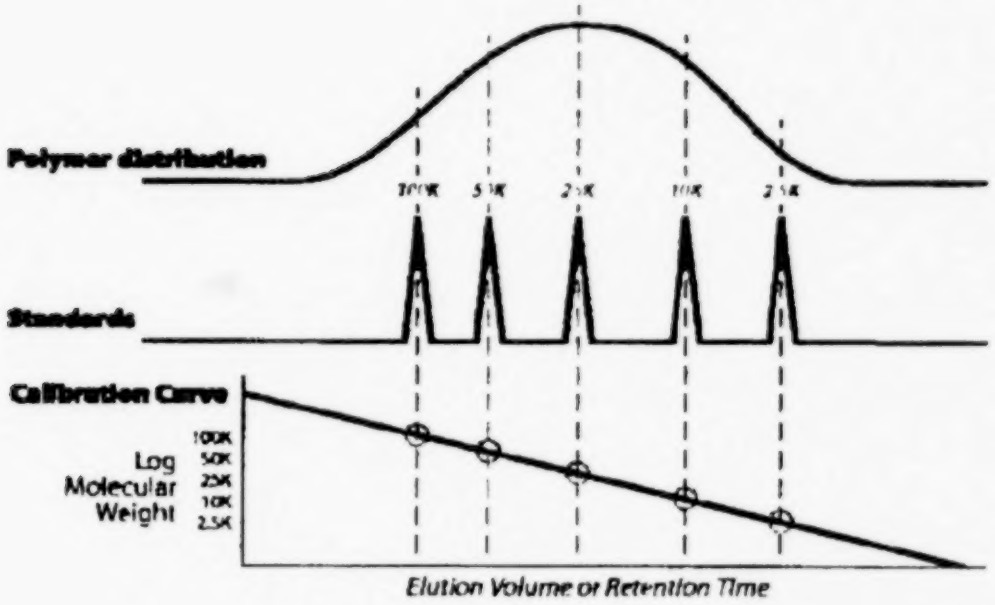
Figure H. Typical SEC chromatogram



42. The molecular weight of the molecules in each fraction can be directly measured using the methods described above, thereby obtaining the molecular weight distribution of the polymer. An easier and more common method, however, is to correlate the elution volume or retention time on the chromatogram to molecular weight through standards that have known molecular weights. This process is also called column calibration. Through the process of column calibration, a calibration curve can be generated by plotting the molecular weights

of standards against their elution volumes or retention times, as shown in Figure I below.

Figure I. Calibration of SEC column



With a calibration curve in place, the molecular weight corresponding to any elution volume or retention time, including the peak average molecular weight, can be read directly off the calibration curve.

43. With a chromatogram and a proper calibration curve, the peak average molecular weight of a polymer can be read without any further calculation. The calibration can also be used to convert the chromatogram into a molecular weight distribution curve.

44. A person of ordinary skill in the art reviewing the patents-in-suit would have understood Figure 1 to have been created by transforming a chromatogram from a size exclusion chromatography ("SEC") analysis.

45. A person of skill in the art would have understood that, on a chromatogram, for any given elution volume (e.g. from V_1 to V_2) or time interval (e.g. from t_1 to t_2)[13], which is represented by a vertical "slice" on the chromatogram, the width represents the volume and the height represents the concentration of the polymer within that volume. Therefore, the area of the "slice" represents the weight of the polymer eluted during that time interval, and the area under the entire chromatogram curve represents the total weight of the polymer in the entire sample analyzed. The weight percentage of the polymer eluted during that time interval is the area of the "slice" divided by the total area under the curve. A person of skill in the art would have understood that, because this weight percentage corresponds to a time range of t_1 to t_2, which in turn corresponds to a molecular weight range, in order to generate a molecular weight distribution curve such as those in Figure 1, a single time point has to be picked from the time range to represent the range. This single time point can be, for example, t_1, t_2, or $(t_1 + t_2)/2$.

46. A person of skill in the art would have understood that the time point that corresponds to the peak of the original chromatogram (i.e., t_p) must fall within a time interval (e.g., $t_1 < t_p < t_2$). Unless the original peak happens to be the same as the single time point picked for the purpose of generating the molecular weight distribution curve such as those in Figure 1, the original peak will be

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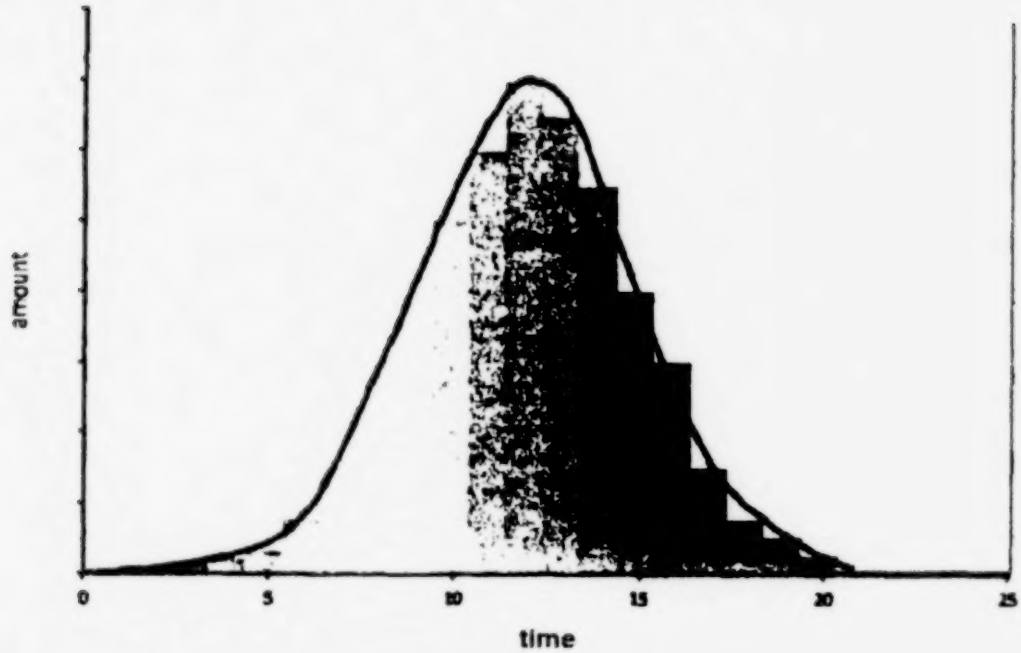
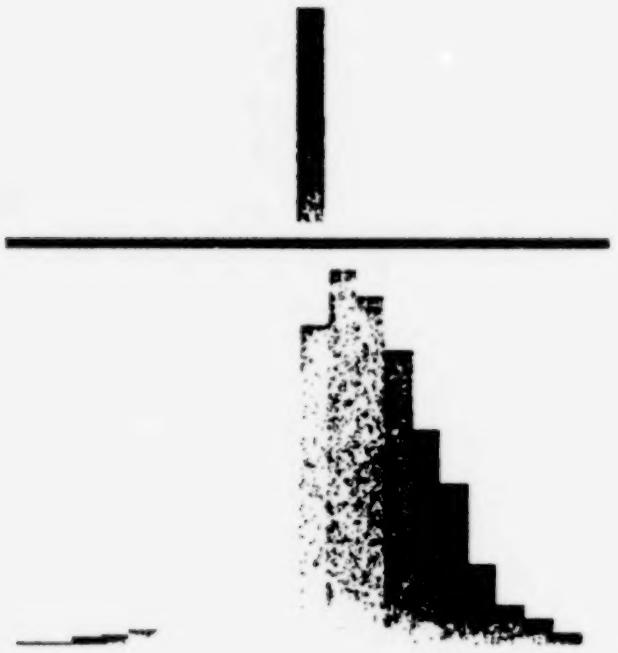
[13] Assuming a constant flow rate, a time interval can be related to a volume. Therefore, for simplicity, I will refer to time interval in the subsequent paragraphs.

represented by a different time point/molecular weight on the molecular weight distribution curve. A person of skill in the art would not logically pick t_1 to represent the time interval because the very first time interval on the chromatogram starts from 0, which does not correspond to any molecular weight. If t_2 is picked to represent the time interval that contains t_p, because t_2 represents a lower molecular weight than t_p, the peak will be shifted to the lower molecular weight side; if $(t_1+t_2)/2$ is picked to represent the time interval that contains t_p, then the peak could be shifted to either the lower or higher molecular weight side depending on whether t_p is smaller or larger than $(t_1+t_2)/2$.

47. This process can be represented graphically as follows. On a chromatogram from a calibrated SEC column, the elution time is correlated with molecular weight. The percentage of the sample at particular molecular weights can be determined by integrating the area under sections of chromatogram, i.e., vertically dividing it into evenly spaced slices, which are shown on the graph below as rectangles, each of which has a unique color.



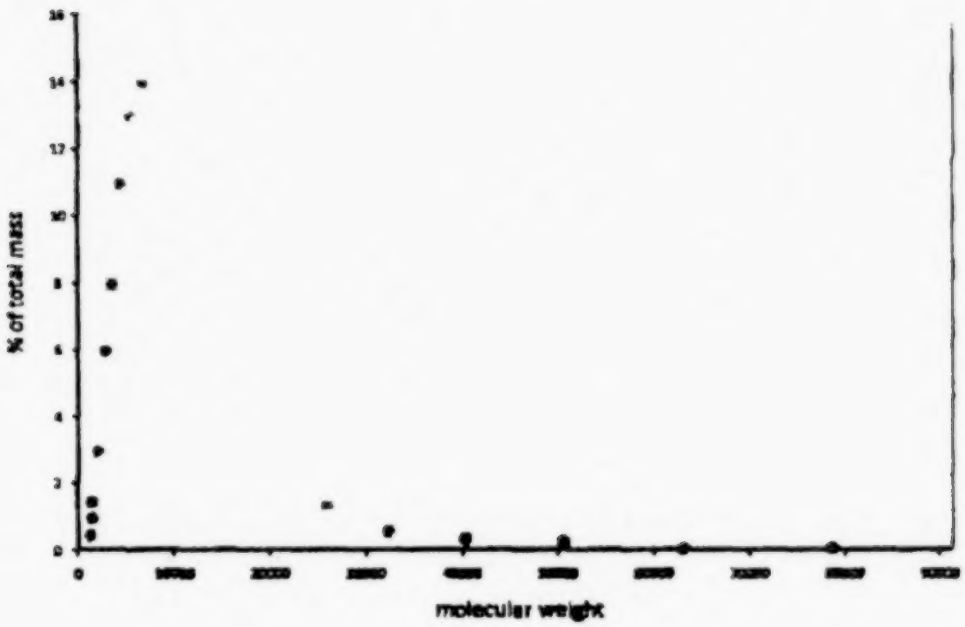
48. The percentage of the entire copolymer sample represented by each slice would then be calculated. This can be easily accomplished by determining the area of a slice and dividing it by the area of all of the slices of the chromatogram, and multiplying that result by 100, as depicted in the figure below:



x 100

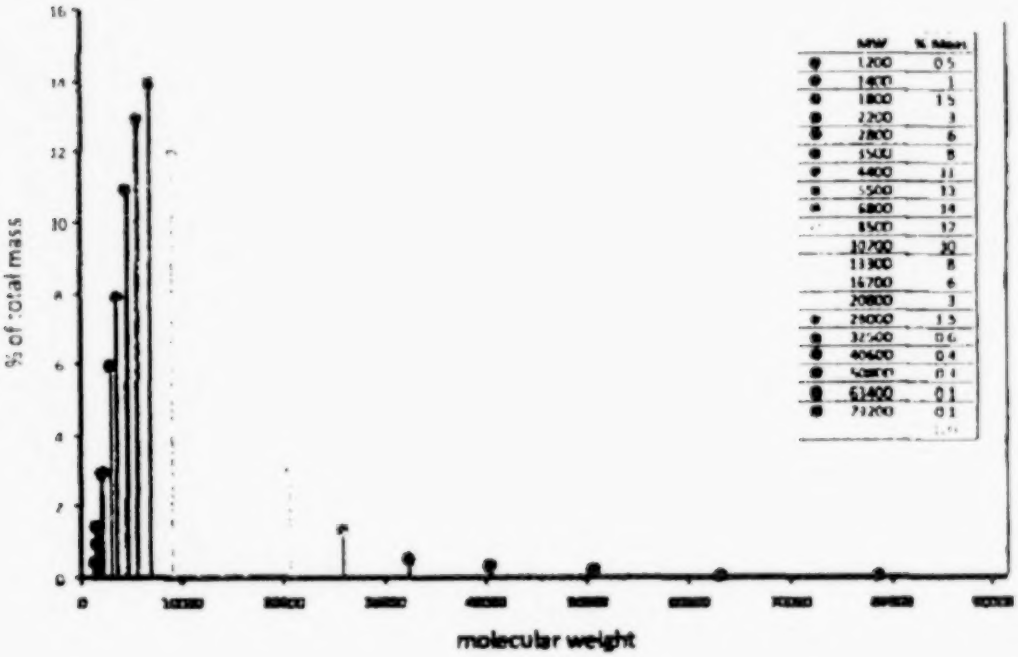
This calculation provides the percentage of all of the molecules represented by the sixth (blue) rectangle from the right compared to all of the molecules in the sample. The area of each slice represents the total amount of copolymer coming out of the column over that time.

49. Repeating the process for each slice and plotting the results on a graph of percent of total mass versus molecular weight provides a data point for each slice as shown in the figure below:



This figure represents the percent of copolymer molecules at the molecular weight associated with each slice, as determined by the calibration curve.

50. When the percentages for each slice are added, the sum equals 100%. Thus, the curve accounts for 100% of the polymer molecules in the sample.



51. The data points can be connected, resulting in a curve similar to the 7.7 kDa curve in Figure 1 of the patents in suit.

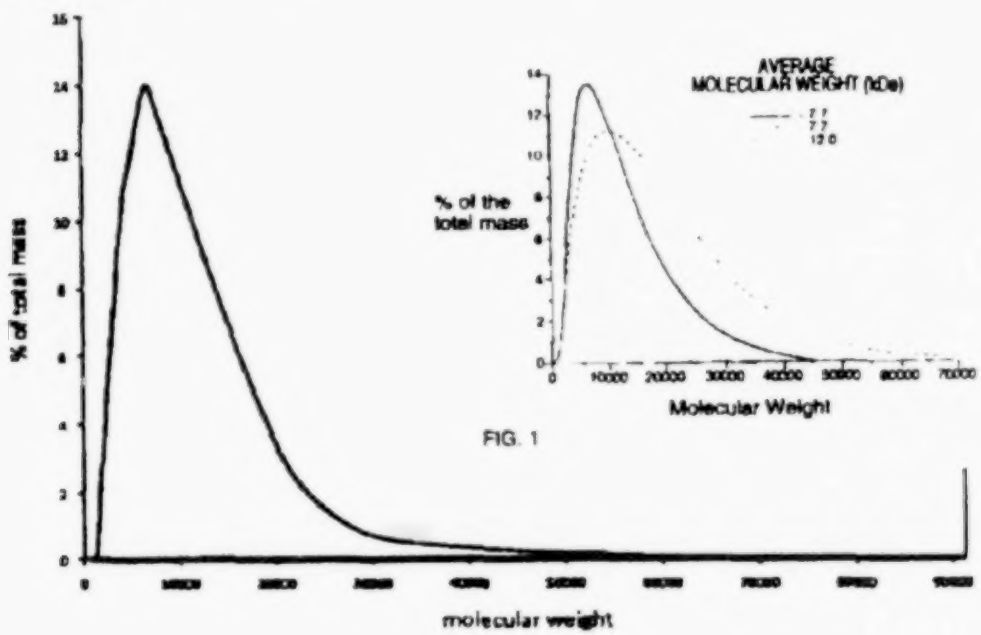


FIG. 1

52. Thus, it would have been expected that the peak of the molecular weight distribution curves would shift slightly from the value read from the peak of the chromatogram. The reason for this shift is depicted in the figure in paragraph 47 above. The peak falls somewhere within the largest green rectangle, but when the area of the rectangle is calculated, the entire rectangle must be attributed to a single molecular weight value. As I previously explained, the area of the green rectangle can be attributed to the left side of the rectangle, at a higher molecular weight than the peak, or to the right side of the rectangle, at a lower molecular weight than the peak, or to some point in the middle of the rectangle. The point is that it is unlikely that the same molecular weight value as the peak molecular weight would be given to the largest rectangle, and thus it is likely that the peak would shift slightly.

53. The degree of the shift would depend on the technique used to create Figure 1, in particular the number of data points generated and the time or volume value on the chromatogram selected to generate a particular mass percent data point.

IX. CLAIM CONSTRUCTION

54. In the paragraphs that follow, I set forth my opinion as to the proper interpretation of phrases or terms in the claims of the patents-in-suit by the person of ordinary skill in the art to which the claims of the patents are directed.

55. I understand that Teva is asserting claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1-6 of the '898 patent, claims 1-6 of the '430 patent,

claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1-8 of the '847 patent, claims 1-33 of the '539 patent, and claims 1-20 of the '098 patent.

A. Copolymer-1

56. The term "copolymer-1" is defined in the specification. Specifically, the specification describes copolymer-1 as "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively." See the '808 patent, col. 1, lines 32-34.

57. A person of skill in the art would have understood that copolymer-1 is made by a process in which the four carboxyanhydride amino acids are mixed together with no external guidance as to the amino acid sequence of the resulting polypeptides. A person of skill in the art would have understood that the specific amino acid sequence and the number of amino acids in any given polypeptide making up copolymer-1 cannot be predicted because of the complex nature of the interactions among the four amino acids. The result of the above polymerization is a complex mixture of many polypeptide species. Although it is possible that some of the polypeptide species might happen to have the same amino acid makeup (sequence and number of residues), a person of skill in the art would have understood that the mixture, as a whole, is non-uniform with respect to amino acid sequence as well as the number of amino acid residues. Because the molecular weight of a polypeptide is the sum of its amino acid residues, a person of skill in the art would have understood that the polypeptides comprising copolymer-1 are also non-uniform with respect to molecular weight.

58. Examples 3 and 4 of the patents-in-suit, as well as the references cited therein, clearly explains that copolymer-1 is synthesized by polymerizing the carboxyanhydrides of four amino acids and protected amino acids. See Exhibit E, Teitelbaum, p. 243, section 2.3.1.

59. Therefore, in my opinion, the term "copolymer-1" would have been understood by a person of skill in the art to mean "a complex mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides."

B. Protected copolymer-1

60. A person of ordinary skill in the art would understand "protected copolymer-1" as copolymer-1 in which at least one of the amino acids has a protecting group. Example 3 of the patent describes "protected copolymer-1" as the product of polymerization of four amino acids, two of which have protecting groups. '808 patent, col. 4, lines 30-38. There is nothing in the patents that would require the addition of any language regarding whether the "composition" of protected copolymer-1 would "vary" from batch to batch. Thus, in my opinion, the proper construction of "protected copolymer-1" means copolymer-1 containing one or more protecting groups on one or more amino acids.

C. Copolymer-1 composition

61. The term "composition" in the context of the patents-in-suit has an ordinary meaning of "a product of mixing or combining various elements or ingredients." See Webster's Ninth New Collegiate Dictionary, 1988, p. 270 (attached as Exhibit G). In the context of copolymer-1, copolymer-1 itself can be a composition because it includes polypeptides of various sizes. Further, by definition the composition can also include other components. Thus, in my opinion, the term "copolymer-1 composition" would have been understood by a person of skill in the art to mean "copolymer-1, optionally in combination with other substances."

D. Copolymer-1 fraction

62. The patents describe two methods for making copolymer-1 fractions having the claimed molecular weight ranges. First, they describe fractionation of copolymer-1 containing high molecular weight species. '808 patent, col. 2, line 29-36. Second, they describe preparing a copolymer-1 fraction directly upon removing the protection from the amino acids. '808 patent, col. 2, lines 36-40. In my opinion, a person of skill in the art would have understood the term "fraction" to have its ordinary meaning of portion, and therefore would have understood the term "copolymer-1 fraction" to mean "a portion of the polypeptides that make up copolymer-1," which could be made by either method described in the patents.

E. Molecular weight

63. In my opinion, the term "molecular weight," unmodified by terms that would imply an average molecular weight, such as when referring to individual molecular species, would be understood by a person of skill in the art to have its ordinary meaning of "the sum of the atomic weights of the atoms making up a molecule."

F. Copolymer-1 having a molecular weight

64. The person of skill in the art would have understood that because copolymer-1 is a mixture of polypeptides that are non-uniform with respect to molecular weight, it cannot have "a" molecular weight. A person of skill in the art would have understood that "copolymer-1 having a molecular weight" means copolymer-1 having an average molecular weight.

65. Further, in the context of claim 1 of the '808 patent and claim 1 of the '589 patent, where the term appears, the copolymer-1 recited in the claims has a molecular weight of about 5 to 9 kilodaltons. This molecular weight range coincides with the "7000 ± 2000 Da" disclosed in Example 4 of the specification. See the '808 patent, col. 4, lines 62-65 and col. 5, lines 3-5. A person of skill in the art would have understood that copolymer-1 prepared according to the method of Example 4 would include species that have individual molecular weights that are either below or above the range of about 5 to 9 kilodaltons. Therefore, a person of skill in the art would not have understood the term "molecular weight" to mean the

individual molecular weight of all species within the copolymer-1.

66. Therefore, in my opinion, the term "copolymer-1 having a molecular weight" would have been understood by a person of skill in the art to mean "copolymer-1 having an average molecular weight," which further means "copolymer-1 having a peak molecular weight detected using an appropriately calibrated suitable gel filtration column." See paragraph 77 for interpretation of "average molecular weight."

G. Molecular weight range

67. The ordinary meaning of the term "range" is "a set of values between an upper boundary and a lower boundary." Therefore, in my opinion, the term "molecular weight range" would have been understood by a person of skill in the art to mean "a set of molecular weights between an upper boundary and a lower boundary."

H. Molecular weight profile

68. The term "molecular weight profile" appears in col. 2, lines 29-30 and 36-40 in the '808 patent and in the context of "copolymer-1 with the desired molecular weight profile." Viewed in the context of the Specification, the paragraph in which the term appears follows the first three paragraphs under Detailed Description of the Invention. In these three paragraphs, the characteristics of the copolymer-1 of the invention are described in various ways, for example, in certain percentages of species having a molecular weight above a certain level, in having

certain percentage of the polymer molecules within a certain molecular weight range, and in having an average molecular weight within certain ranges. See the '808 patent, col. 1, line 64-col. 2, line 13. The specification also provides actual examples of how copolymer-1 with these molecular weight characteristics can be made. Therefore, the "desired molecular weight profile" should be interpreted to include all of the aforementioned molecular weight characteristics, and the term "molecular weight profile" would have been understood by a person of skill in the art to mean "molecular weight characteristics of a sample."

I. Molecular weight distribution

69. In his polymer chemistry textbook, Flory defines molecular weight distribution as "knowledge of the mole or weight fraction of each species." See Exhibit F, Flory, Principles of Polymer Chemistry, 1953, p. 317. This definition is equivalent to "a description of the relationship between the quantity of molecules and the molecules' respective molecular weights," which would be what a person of skill in the art would have understood the term "molecular weight distribution" to mean. This understanding is supported by the use of the term in the claims and the specification. For example, the specification refers to Figures 1 and 2 as showing a molecular weight distribution. See the '808 Patent, col. 1, lines 56-59. The figures provide "a description of the relationship between the quantity of molecules and the molecules' respective molecular weights." Thus, the term "molecular weight distribution" would have been understood by a person of skill in the art to

mean "a description of the relationship between the quantity of molecules and the molecules' respective molecular weights."

J. Average molecular weight

70. Example 1 of the specification states that the molecular weight distribution of copolymer-1 was determined on a calibrated gel filtration column, specifically a Superose 12 column, using a UVIKON spectrophotometer. See the '808 Patent, col. 3, lines 3-8. As such, a person of skill in the art would have understood that the method of determining molecular weight distribution was size exclusion chromatography, and that a calibration curve was generated to correlate molecular weight with elution volume or retention time. Example 1 also describes the average molecular weights of the batches that were analyzed by SEC. I note that peak molecular weight, also called peak average molecular weight, is the molecular weight at the highest point of a chromatogram. Peak molecular weight can be obtained directly from the chromatogram and the calibration curve, but further data manipulation and calculation is needed to calculate either the weight average molecular weight or the number average molecular weight. The specification does not describe the calculation of the average molecular weight, which would have indicated to the person of skill in the art that the average molecular weight referred to is a peak molecular weight.

71. A person of skill in the art would have understood the ordinary meaning of "average" to be "a single value (as a mean, mode, or median) that summarizes or represents the general significance of

a set of unequal values," and the ordinary meaning of "mode" in this definition is "the most frequent value of a set of data" (see Webster's Ninth New Collegiate Dictionary, 1988, pp. 119, 762, Exhibit H). Therefore, the ordinary meaning of "average molecular weight" would include "the most frequent value of molecular weight that represents the general significance of a set of unequal individual molecular weights of species within a sample," which is precisely the peak molecular weight.

72. Further, according to the specification, Figure 1 displays the molecular weight distribution of three batches of copolymer-1. See the '808 Patent, col. 1, lines 57-59. The legend of both Figure 1 and Figure 2 indicates that the batches have "average molecular weights" of 7.7, 7.7, and 12.0 kDa. The peaks of the curves drawn in Figure 1 are close to those numbers, which would support the understanding that the numbers in the legend were peak molecular weights.[14] A person of skill in the art would have understood that the molecular distribution curves in

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[14] The peak positions of the curves in Figure 2 were not considered by me and would not have been considered by a person of skill in the art because they have no bearing on the meaning of "average molecular weight." That is because the peak molecular weight detected using a gel filtration column occurs at the apex of the original chromatogram, which corresponds to a fraction that contains the largest amount of polymer (see paragraph 47 above). Because the amount of polymer detected by the UV detector is based on mass rather than on number of moles, when the chromatogram is transformed into a molecular weight distribution curve, the peak of the chromatogram would correspond to the peak of a mass fraction vs. molecular weight curve, such as those in Figure 1, rather than a molar fraction vs. molecular weight curve, such as those in Figure 2.

Figure 1 are transformed from SEC chromatograms, and that the process of transferring the data from the chromatogram would likely cause the peak on each curve to shift slightly. Each curve in Figure 1 is identified with an average molecular weight. On the curves identified with an average molecular weight of 7.7 kDa, I measured the peak to be at 6.8 kDa[15]; on the curve identified with an average molecular weight of 12 kDa, I measured the peak to be at 11 kDa. A person of skill in the art would have understood that the peak positions on the curves are within a margin of error of the corresponding identified average molecular weights.

73. A person of skill in the art, knowing that there are other average molecular weights that are used to describe polymers, could also have considered the possibility that the term "average molecular weight" refers to number average molecular weight M_n or weight average molecular weight M_w. However, a person of skill in the art would have understood that, on a molecular weight distribution curve, M_n typically is smaller than M_p. *See, e.g.*, Handley, Chapter 6, Chromatographic methods, in Polymer Characterisation, Edited by Hunt and James, pp. 145-156, 1993 (Exhibit I) and Smigol *et al.*, Monodisperse polymer beads as packing material for high-performance liquid chromatography, *Die Angewandte Makromolelulare Chemie*, 195 (1992), pp.151-164 (Exhibit J). These references provide

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[15] I note that the minor tick between 0 and 10000 on the x-axis of Figure 1 is not at the halfway point and therefore does not correspond to a molecular weight of 5000. Accordingly, the peak position on the x-axis was determined based on the major tick at 10000.

further support for the understanding that M_n would be less than M_p for polymer distributions of the type shown in the patents-in-suit. For example, Figure 6.3 on page 148 of Exhibit I shows a typical molecular weight distribution curve (see page 147, last paragraph), in which M_n is less than M_p. Figure 4 on page 160 of Exhibit J show molecular weight distribution curves of polystyrene and poly(methyl methacrylate). In both curves, M_n is to the left of the peak, which means the value of M_n is less than that of M_p. Because M_n would have been understood to be less than M_p, a person of skill in the art would not have interpreted the term "average molecular weight" in the legend of Figure 1 to mean M_n, i.e., number average molecular weight. Therefore, if the "average molecular weights" referred to in Figure 1 were M_n, the person of skill would have expected the peak on the curve to have a higher value than 7.7 (or be shifted to the right of 7.7), not a lower value. For this reason, a person of skill in the art would not have interpreted the term "average molecular weight" to mean M_n.

74. Based on Figure 1, a person of skill in the art would also have been able to tell that the corresponding M_w for both the 7.7 and 12.0 kDa curves would be larger than the average molecular weights stated in the legend, and therefore would not have interpreted the term "average molecular weight" to mean Mw. Although, during the prosecution of the '847 patent (which does not include any claim that recites "average molecular weight"), the applicants stated that "kilodalton units implies a weight average molecular weight," (see the '847 patent prosecution history, 6/26/2002

Amendment (attached as Exhibit K), page 3 [TEV000304498]), a person of skill in the art would have understood that to be a misstatement because kilodalton is the unit for any measurement of molecular weight[16], not just M_w, and the person of skill would have recognized that Mw would very likely be greater than stated in the Figures based on the information provided in the curves.

75. A person of skill in the art would not understand "average molecular weight" to mean number or weight average for the additional reason that it is common practice for those two averages to be listed together when referencing data generated by SEC, so that a polydispersity index can be calculated. It is uncommon in my experience for only one of M_n or M_w to be listed when referencing data generated by SEC.

76. During the prosecution of the '539 patent, in response to the Patent Examiner's rejection of the term "average molecular weight" based on indefiniteness, the applicants explained that "average molecular weight" refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1. See Exhibit L, the '539 patent prosecution history, 12/1/2004 Amendment, page 10 [TEV000304803]. Based on the information provided in the patents-in-suit, a person of skill in the art would have accepted this interpretation as being accurate.

77. For the reasons stated above, the term "average molecular weight" would have been

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[16] See footnote 2 above.

understood by a person of skill in the art to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column."

K. Predetermined by test reaction

78. In my opinion, the term "predetermined" would have been understood by a person of skill in the art to have an ordinary meaning of "determined beforehand." See Webster's Ninth New Collegiate Dictionary, 1988, p. 926 (attached as Exhibit M). In the context of the patents-in-suit, the test reaction is conducted for a specific purpose, namely to study the effects of varying reaction conditions, e.g., time and temperature, on the results of the reaction, e.g., the molecular weight of the product. Example 4 of the specification states that "a test reaction is performed on every batch at different time periods for example, from 10-50 hours." See the '808 patent, col. 4, lines 65-67. Example 4 further states that "[t]he results concerning the molecular weight of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed ... is calculated from the curve and performed on larger scale reaction." See the '808 patent, col. 5, lines 1-5. However, Example 4 does not state or indicate the small scale reaction is performed on the same batch of protected copolymer-1 used in the "larger scale reaction." As such, a person of skill in the art would have understood that the test reactions could be performed on a separate batch and there may not necessarily be a corresponding "large scale" reaction for every test reaction. Indeed, a person of skill in the art would have understood that the knowledge

obtained from any test reaction could be applied to other reactions performed under similar conditions later. In my opinion, a person of skill in the art would have understood the term "test reaction" to mean "reaction carried out to determine results of varying reaction conditions." Therefore, a person of skill in the art would have understood the phrase "predetermined by test reaction" to mean "determined beforehand by a reaction carried out to determine results of varying reaction conditions."

L. Selecting a predetermined molecular weight profile

79. I have provided my opinions regarding how a person of ordinary skill in the art would have understood the terms "predetermined" and "molecular weight profile" above. In my opinion, a person of ordinary skill in the art would have understood the phrase "selecting a predetermined molecular weight profile" to mean "choosing molecular weight characteristics of a sample that are determined beforehand."

M. Over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa

80. As stated in paragraph 26 above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture.[17] Therefore, in my opinion, the term "over

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[17] The term "molecular weight" means "the sum of the atomic weights of the atoms making up a molecule" because the term is

75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" would have been understood by a person of skill in the art to have an ordinary meaning of "over 75% of molecules in a sample, as compared to the total number of molecules in the sample, have molecular weights greater than about 2 kilodaltons and less than about 20 kilodaltons."

N. Over 75% of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of 2 kDa to 20 kDa

81. As stated above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Therefore, in my opinion, the term "over 75% of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of 2 kDa to 20 kDa" would have been understood by a person of skill in the art to have an ordinary meaning of "over 75% of copolymer molecules in the mixture, as compared to the total number of copolymer molecules in the mixture, have molecular weights greater than 2 kilodaltons and less than 20 kilodaltons."

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being used to delineate the molecular weight limits of the claimed range. This claim term therefore refers to the percentage of polypeptides in which the individual polypeptide molecules have individual molecular weights (i.e., the sum of the atomic weights of the atoms making up the polypeptide molecule) that are above or below the stated numerical molecular weight values. This opinion applies to the use of the term "molecular weight" in the claims terms addressed in paragraphs 80-88.

O. Over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons

82. In my opinion, the term "over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "over 75% of polypeptides in the mixture, as compared to the total number of polypeptides in the mixture, have molecular weights greater than about 2 kilodalton and less than about 20 kilodaltons."

P. Over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons

83. In my opinion, the term "over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "over 75% of molecules making up copolymer-1 in the fraction have molecular weights greater than about 2 kilodaltons and less than about 20 kilodaltons.

Q. Less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons

84. In my opinion, the term "less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 5% of the molecules making up copolymer-1 have molecular weights greater than 40 kilodaltons."

R. Less than 5% of the copolymers have a molecular weight above 40 kDa

85. In my opinion, the term "less than 5% of the copolymers have a molecular weight above 40 kDa" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 5% of the copolymer molecules have molecular weights greater than 40 kilodaltons."

S. Less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons

86. As stated above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Therefore, in my opinion, the term "less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of

"less than 5% of the total number of polypeptides in the mixture have molecular weights greater than 40 kilodaltons."

T. Less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons

87. As stated above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Therefore, in my opinion, the term "less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 2.5% of the total number of polypeptides in the mixture have molecular weights greater than 40 kilodaltons."

U ess than 2.5% of the copolymers in the mixture have a molecular weight above 40 kDa

88. In my opinion, the term "less than 2.5% of the copolymers in the mixture have a molecular weight above 40 kDa" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 2.5% of the copolymer molecules have molecular weights greater than 40 kilodaltons."

V. The molecular weight range claim terms

89. In my opinion, a person of skill in the art would have understood the term "about" to have its ordinary meaning of approximately, and would have understood the actual numbers and unit of kilodalton to have their customary meanings. Specifically, a person of skill in the art would have understood the term "6.25 to 8.4 kilodaltons" to mean "6.25 to 8.4 kilodaltons," the term "about 4 to about 8.6 kilodaltons" to mean "approximately 4 to approximately 8.6 kilodaltons," the term "4 to 8.6 kDa" to mean "4 to 8.6 kilodaltons," the term "about 5 to about 9 kilodaltons" to mean "approximately 5 to approximately 9 kilodaltons," the term "about 5 to 9 kilodaltons" to mean "approximately 5 to 9 kilodaltons", the term "about 4 to about 9 kilodaltons" to mean "approximately 4 to approximately 9 kilodaltons," the term " 7000 Da ± 2000 Da" to mean "5 to 9 kilodaltons," the term "4 to 8 kDa" to mean "4 to 8 kilodaltons," the term "7 to 8 kDa" to mean "7 to 8 kilodaltons," the term " 7.7 kDa" to mean "7.7 kilodaltons," the term "about 7.7 kDa" to mean "approximately 7.7 kilodaltons," and the term "greater than about 8.6 kilodaltons" to mean "more than approximately 8.6 kilodaltons."

I declare under penalty of perjury that the factual statements contained herein are known by me or believed by me to be correct.

DATED: April 19, 2010

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Dr. Gregory A. Grant

[Exhibit A omitted]

Exhibit B.

United States Patent [19]

[11] Patent **Number: 5,800,808**

Konfino et al.

[45] **Date of Patent: Sep. 1, 1998**

[54] **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

[75] Inventors: **Eliezer Konfino**, Ramat Gan; **Michael Sela**, Rehovot; **Dvora Teitelbaum,** Rehovot; **Ruth Anion**, Rehovot, all of Israel

[73] Assignee: **Veda Research and Development Co., Ltd.**, Rehovot, Israel

[21] Appl. No.: **447,146**

[22] Filed: **May 22, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 344,248, Nov. 23, 1994, abandoned, which is a continuation of Ser. No. 248,037, May 24, 1994, abandoned.

[51] **Int. CI.** **A61K 27/00**

[52] **U.S. CI**.....**424/78.08**; 424/78.26; 424/78.29; 514/561; 525/420; 525/434; 525/435; 528/328

[58] **Field of Search** 424/78.29, 78.08,424/78.26; 514/561; 525/420. 434, 435; 528/328

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[OTHER PUBLICATIONS OMITTED]

Primary Examiner—Frederick Krass

Attorney, Agent, or Firm—Kenyon & Kenyon

[57] **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

1 Claim, 2 Drawing Sheets

[OTHER PUBLICATIONS OMITTED]

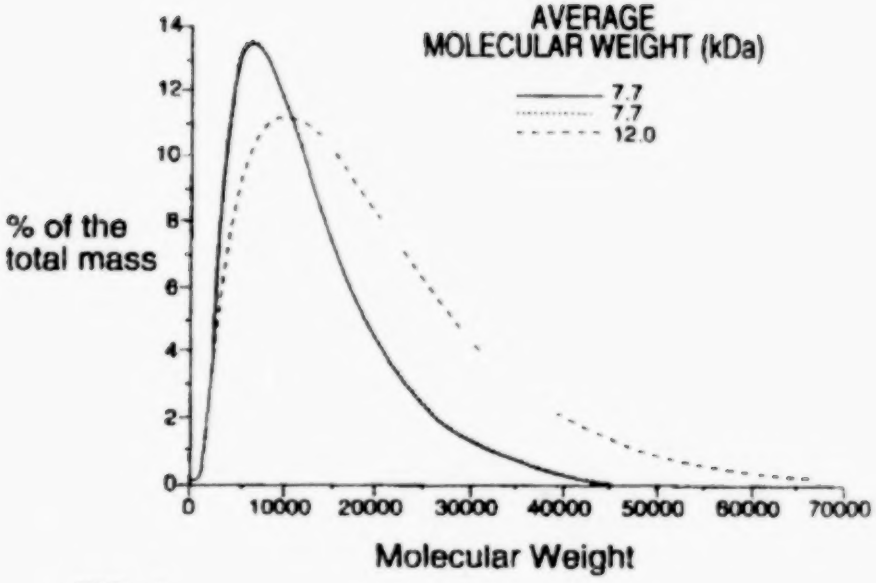

FIG. 1

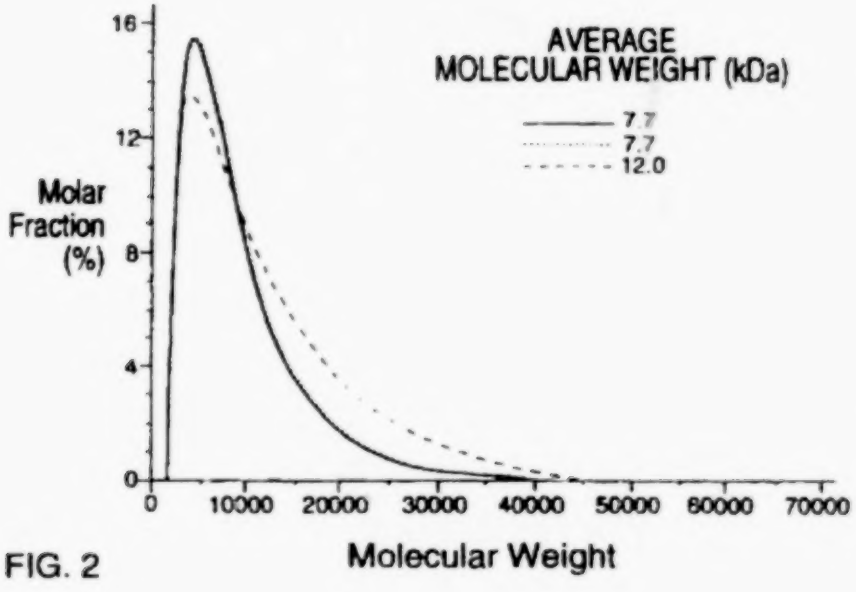

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248.037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot. Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3.849.550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical com-position and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa. FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition

contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat No. 3.849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, y-benzyl glutamate and E-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the y-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20° to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for subcutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic method of preparation of low-toxicity copolymer-1 Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3.849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel nitration, FRACTOGEL TSK HW55 (600x26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg/ml, in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an average molecular weight of 7-8 KDa was isolated between 120-130 minutes (Batch A).

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total

copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A: In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic" If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic"

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end

of 48 hours, and it was consequently designated "toxic"

B: In Vitro

RBL—Degranulation test

I. Introduction

Histamine (or serotonin) release from basophile is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-2H3) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (E. L. Basumian, C. Isersky, M. G. Petrino and R. P Siraganian. Eur. J. Immunol. 11. 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P Siraganian. Trends in Pharmacological Sciences. October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects.

II. Principle of the test method

Rat Basophilic Leukemia cells (RBL-$2H_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100

μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250-14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the 15 following table.

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g),

alanine (50 g), y-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydro-bromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), τ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20°-28° C. a test reaction is performed on every batch at different time periods for example, from 10-50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2.000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of low-toxicity copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°-20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5-6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

What is claimed is:

1. A method of manufacturing copolymer-1, comprising reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1, treating said trifluoro-acetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : **5,800,808**

DATED : **September 1, 1998**

INVENTOR(S) : **Konfino, et al**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 1, right column, line 1, change "onExperimen-" to --on Experimen- --

Page 1, right column, line 23, change "Automimmunity" to --Autoimmunity--;

Page 2, left column, line 27, change "1983, pp." to --1983, 42, pp.--;

Page 2, left column, line 14 from bottom, change "1985," to --1985, 35,--;

Page 2, right column, lines 8 and 9, change "The....Sclerosis" to --"The....Sclerosis"--;

Page 2, right column, lines 17 and 18, change "Copolymer 1 ...(letter)" to --"Coploymer 1... (letter)"--;

Column 1, line 8, change "1994, pp." to --1994, 1, pp. -;

Column 1, line 34, change "Marland" to --Maryland--;

Column 1, lines 35 and 36, delete "Tel-Aviv University, University of Marland School of Medicine,";

Column 2, line 17, change "y-benzyl to --*y*-benzyl--;

Column 2, line 20, change "y-benzyl to --*y*-benzyl--;

Column 4, line 33, change "y-benzyl to --*y*-benzyl--;

Column 4, line 52, change "r-benzyl to --*y*-benzyl--;

Column 4, line 60, change "omega" to --gamma--;

Signed and Sealed this

Third Day of April, 2001

Attest: /s/ Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer *Acting Director of the United States Patent and Trademark Office*

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	:	5,800,808
APPLICATION NO.	:	08/447146
DATED	:	September 1, 1998
INVENTOR(S)	:	Konfino et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the face of the patent, # (73) Assignee, change "Veda" to --Yeda--.

Signed and Sealed this

Twenty-second Day of May, 2007

/s/ Jon W. Dudas

JON W. DUDAS

Director of the United States Patent and Trademark Office

[REMAINDER OF EXHIBIT B OMITTED]

[EXHIBITS C-M OMITTED]

OPPOSITION BRIEF

No. 13-854

In The Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA NEUROSCIENCE, INC., AND YEDA RESEARCH AND DEVELOPMENT CO., LTD., PETITIONERS

v.

SANDOZ INC., MOMENTA PHARMACEUTICALS INC., MYLAN PHARMACEUTICALS INC., MYLAN INC., AND NATCO PHARMA LTD.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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FEBRUARY 5, 2014

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QUESTION PRESENTED

Whether Federal Rule of Civil Procedure 52(a) requires an appellate court reviewing a district court's construction of patent claims to defer to conclusions that are based on a litigation expert's declaration that expressly contradicts the patent record.

CORPORATE DISCLOSURE STATEMENT

Sandoz Inc. is an indirect wholly-owned subsidiary of Novartis AG. No other publicly held company owns 10% or more of the stock of Sandoz Inc.

Momenta Pharmaceuticals Inc. is a publicly held corporation. No parent corporation or publicly held corporation owns more than 10% of its stock.

Mylan Inc. is a publicly held corporation. No parent corporation or publicly held corporation owns more than 10% of its stock. Defendant Mylan Pharmaceuticals Inc. is wholly owned by Mylan Inc.

Natco Pharma Ltd. is a publicly held corporation. No parent corporation or publicly held corporation owns more than 10% of its stock.

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INTRODUCTION

Petitioner makes the extraordinary request that this Court grant review to consider a question currently being considered by the en banc Federal Circuit. In the 30 years since that Circuit's creation, this Court has never preempted the Circuit's en banc review, and nothing about this case warrants doing so. There is no reason to presume (as Teva does) that this Court's intervention will be needed no matter how the en banc Circuit rules. And this case is not a suitable vehicle to review the question in any event.

Teva sued Sandoz and Momenta (together, Sandoz) and Mylan and Natco (together, Mylan) for infringement of multiple related patents covering Teva's multiple-sclerosis drug, Copaxone® Most of those patents expire on May 24, 2014, but one would have expired on September 1, 2015. The district court held all of the asserted claims valid and infringed, but the court of appeals held certain of the asserted claims invalid as indefinite, including the sole claim of the patent that would have expired on September 1, 2015. At the same time, the court of appeals upheld the validity of certain claims expiring on May 24, 2014, and it affirmed the finding of infringement with respect to those claims. As a result of that decision, the district court's injunction was modified on remand so that Sandoz and Mylan are enjoined from entering the market until May 24, 2014, rather than September 1, 2015.

The question Teva poses in its petition—whether certain aspects of claim construction in patent cases are entitled to deferential review on appeal—does not warrant this Court's review, at least not at this time and in this case. That question is pending before the en banc Federal Circuit in *Lighting Ballast Control LLC v. Philips Electronics North America Corp.*, Nos. 2012-1014, -1015 (Fed. Cir. reargued Sept. 13, 2013). To the extent there is any conflict within the Federal Circuit, its resolution is appropriately left to that court.

Moreover, even if this Court were inclined to review the appellate standard-of-review question Teva poses, *Lighting Ballast*—or a case applying whatever rule the Federal Circuit adopts in *Lighting Ballast*—would be the appropriate vehicle for that review. In *Lighting Ballast*, the parties and numerous amici have focused on the standard of review and the effect it would have on the outcome of that case. Here, by contrast, Teva did not argue that the standard of review for claim construction should be changed (or even cite Rule 52) until its petition for rehearing. Thus, this case is no better vehicle than *any* claim-construction decision, and in fact is worse than most. The district court here held no evidentiary hearing and observed no live testimony before construing the claims and ruling on their indefiniteness.

Nor would the answer to the question Teva poses change the result in this case. Indeed, the Federal Circuit itself recognized as much, by repeatedly rebuffing Teva's requests to hold this case pending its en banc decision in *Lighting Ballast*. Even under

Teva's proposed standard, there were no factual findings in this case to which the Federal Circuit could properly have deferred. The "facts" as to which Teva seeks deference do not involve the historical meaning of any claim term. Rather, those "facts" are simply Teva's litigation expert's "interpretation" of the patent documents themselves—that is, the patents and their prosecution history. Indeed, deference would be particularly unwarranted here because Teva's expert simply labeled the patent documents mistaken wherever they did not support Teva's litigation position. Regardless of the standard of review, a reviewing court in a patent case should read the legal documents in the patent record for itself and disregard extrinsic evidence contrary to that record.

As a last resort, Teva asks this Court to hold its petition pending the resolution of *Nautilus, Inc. v. Biosig Instruments, Inc.*, No. 13-369 (cert. granted Jan. 10, 2014). But a hold is unwarranted. The question Teva presents is unrelated to the questions presented in *Nautilus*—which concern the substantive standard for indefiniteness, not the standard for appellate review. Having so framed its question, Teva is precluded from obtaining relief based on that case. Nor could *Nautilus* affect the outcome of this case in any event. In *Nautilus*, the petitioner contends that the Federal Circuit's substantive standard for indefiniteness—under which claims are invalid for indefiniteness only where "insolubly ambiguous" or "incapable of construction"—is too favorable to patentees and thus results in patent claims being

upheld that should be struck for indefiniteness. Given that Teva's claims could not even survive under the Federal Circuit's current indefiniteness standard, they *a fortiori* would not survive under any stricter standard this Court might adopt in *Nautilus*.

The petition should be denied.

STATEMENT

A. Statutory Framework

1. Congress enacted the Hatch-Waxman Act to facilitate entry of competitors in the marketplace for pharmaceutical drugs. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585. The Act created an abbreviated new drug application (ANDA) process. This allows the Food and Drug Administration (FDA) to approve drugs that are biologically equivalent to already-approved pharmaceuticals without requiring additional evidence of safety and efficacy. *See* 21 U.S.C. § 355(j)(2)(A)(ii), (iv).

As part of the ANDA process, a drug maker must certify that its drug can be marketed without infringing certain patents related to the already-approved drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii)-(viii). As in this case, drug makers seeking ANDA approval often certify that the applicable patents are "invalid or will not be infringed by the manufacture, use, or sale of the [ANDA applicant's] drug." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). The Hatch-Waxman Act allows a patent holder to treat this "Paragraph IV

certification" as an act of infringement and immediately file a patent infringement suit in district court. 35 U.S.C. § 271(e)(2)(A). This process of certification and suit aims to allow drug manufacturers to launch competing products promptly upon the expiration or invalidation of patents protecting the approved drugs. *See Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1676 (2012); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 670-671 (1990).

2. The Patent Act requires that a patent include claims "particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention." 35 U.S.C. § 112(b) (2012) (formerly 35 U.S.C. § 112 ¶ 2). This ensures that the public has clear notice of what constitutes infringement. *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942); *Permutit Co. v. Graver Corp.*, 284 U.S. 52, 60 (1931).

This Court has explained that "[a] patent is a legal instrument, to be construed, like other legal instruments, according to its tenor." *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996) (internal quotation marks omitted). In construing patent claims, courts look to a hierarchy of sources informative of claim meaning. First, courts consider the claim language itself. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). Second, courts look to a patent's specification and prosecution history, which together with the claims form the public record of the patent. *Id.* at 1313. This Court

has explained that "[t]he claims of a patent are always to be read or interpreted in the light of its specifications." *Schriber-Schroth Co. v. Cleveland Trust Co.*, 311 U.S. 211, 217 (1940). And "an invention is construed not only in the light of the claims, but also with reference to the file wrapper or prosecution history in the Patent Office." *Graham v. John Deere Co.*, 383 U.S. 1, 33 (1966); *see Phillips*, 415 F.3d at 1317.

Third, the en banc Federal Circuit has held that courts construing claim terms may consult extrinsic evidence, including expert testimony, dictionaries, and treatises. But use of these sources is limited. "[W]hile extrinsic evidence can shed useful light on the relevant art, * * * it is less significant than the intrinsic record in determining the legally operative meaning of claim language." *Phillips*, 415 F.3d at 1317 (internal quotation marks omitted). Moreover, courts "should discount any expert testimony that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent." *Id.* at 1318 (internal quotation marks omitted).

B. Factual Background

Teva markets Copaxone®, a drug used to treat multiple sclerosis. With no generic alternative on the market, the cost of treatment is roughly $40,000 per year. C.A. JA19635. Sandoz and Mylan each filed ANDAs seeking FDA approval to market their own

versions of the drug. In response, Teva sued Sandoz and Mylan on nine patents that share a common specification. Pet. App. 4a.

Copaxone is a form of copolymer-1. The asserted patent claims cover copolymer-1 and methods of manufacturing it. Pet. App. 4a. Copolymer-1 is not new; it was invented in 1967 and first patented in 1974. C.A. JA49258; C.A. JA344; C.A. JA26052-26053. But the original patent expired before the inventors could market copolymer-1. To obtain new patent protection, Teva asserted that it had improved copolymer-1, making it less toxic but still efficacious, by selecting portions of copolymer-1 with particular "molecular weights" or "average molecular weights." To get that new patent coverage, Teva was required to define precisely the scope of its claimed improvement. *See* 35 U.S.C. § 112(b); *General Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938).

According to Teva, the effectiveness and reduced toxicity of the claimed substance depend on its precise molecular weight. C.A. JA18180, C.A. JA18199. An accurate determination of molecular weight thus was key to defining the claimed substance. But the molecular weight of any particular batch of copolymer-1 can be determined in multiple ways, including weight average molecular weight (M_w), number average molecular weight (M_n), and peak molecular weight (M_p). Pet. App. 4a. Because the "molecular weight" value differs depending on the type of average, a skilled artisan could not know the

bounds of the asserted claims without knowing which type was claimed.

Claim 1 of U.S. Patent No. 5,981,589 is representative of the claims with this "molecular weight" ambiguity:

> Copolymer-1 having *a molecular weight of about 5 to 9 kilodaltons*, made by a process comprising the steps of:
>
> reacting protected copolymer-1 * * * ; and
>
> purifying said copolymer-1, to result in copolymer-1 *having a molecular weight of about 5 to 9 kilodaltons*.

Pet. App. 5a (emphasis added by court of appeals).

Neither the patents' claims nor their common specification identifies the type of "molecular weight" or "average molecular weight" used in the claims. Indeed, the Patent Office twice rejected as indefinite claims reciting "average molecular weight" because that term is "meaningless as a limitation without specifying" the type of molecular weight. C.A. JA3220; C.A. JA3245. In response, Teva provided conflicting and irreconcilable answers, first telling the Patent Office that "average molecular weight" referred to "weight" average molecular weight (C.A. JA3229), and subsequently stating that "average molecular weight" referred to "peak" molecular weight (C.A. JA3258).

C. Proceedings Below

1. Proceedings in the district court

In the district court, Sandoz and Mylan contended that the asserted claims were invalid for indefiniteness because the patents' claims, common specification, and prosecution history provided no guidance as to which type of molecular weight was claimed, even though that information was critical to defining the claimed substance.

The district court nevertheless held that the asserted claims were not indefinite. Although the court acknowledged that the claims "are silent as to the meaning" of "average molecular weight," it construed "average molecular weight" as "peak molecular weight." Pet. App. 42a, 62a. In so doing, the district court relied on declarations of Teva's expert, Gregory Grant, that were prepared for this litigation and that purported to interpret the patents' specification and prosecution history. When the district court ruled, Teva's expert had not testified or been cross-examined in court. Indeed, the district court held no evidentiary hearing and observed no live testimony before construing the claims and ruling on their indefiniteness.

After a bench trial on infringement and other invalidity contentions, the district court held that the products proposed by Sandoz and Mylan would infringe the asserted claims. Pet. App. 75a-78a. The district court then enjoined Sandoz and Mylan from entering the market until expiration of U.S. Patent

No. 5,800,808 (the '808 patent) on September 1, 2015. Pet. App. 78a-81a.

2. Proceedings in the court of appeals

In a unanimous decision, a panel of the court of appeals held that a subset of the asserted claims (the "Group I" claims) were invalid for indefiniteness. Pet. App. 8a. The court recognized that it was "undisputed that Group I claims contain an ambiguity because their plain language does not indicate which average molecular weight measure is intended." Pet. App. 8a. And it rejected Teva's argument that the prosecution history and specification resolved that ambiguity.

As to the prosecution history, the court of appeals concluded that two of Teva's "prosecution statements directly contradict[ed] each other and render[ed] the ambiguity insoluble." Pet. App. 8a-9a. In particular, when prosecuting one patent, Teva overcame an indefiniteness rejection by asserting that one skilled in the art would understand "average molecular weight" to refer to "*peak*" molecular weight. Pet. App. 9a. Yet when prosecuting a related patent, Teva overcame the same objection by asserting that "average molecular weight" meant "*weight*" average molecular weight. Pet. App. 9a.

The court further held that "[t]he specification does not resolve the ambiguity." Pet. App. 9a. Citing Grant's declarations, Teva contended that the specification's reference to the Size Exclusion Chromatography (SEC) method for determining molecular weight implied "peak" molecular weight and that

Figure 1 of the patents confirmed this. Pet. App. 8a-10a. The court of appeals observed that all the experts, including Grant, agreed that "number" average molecular weight and "weight" average molecular weight also can be obtained from the data generated by the SEC method. Pet. App. 10a. Moreover, Figure 1 (reproduced below from the court of appeals' decision) actually contradicted Grant's declarations because "the peaks of the curves in Figure 1 do not correspond to the values denoted as 'average molecular weight' in the figure's legend." Pet. App. 10a. Indeed, the court noted Grant's concession that "the 7.7 kDa value [stated in Figure 1] is closer to the M_w than to the M_p of the corresponding batch," which refuted Teva's contention that peak molecular weight was the intended measure. Pet. App. 10a.

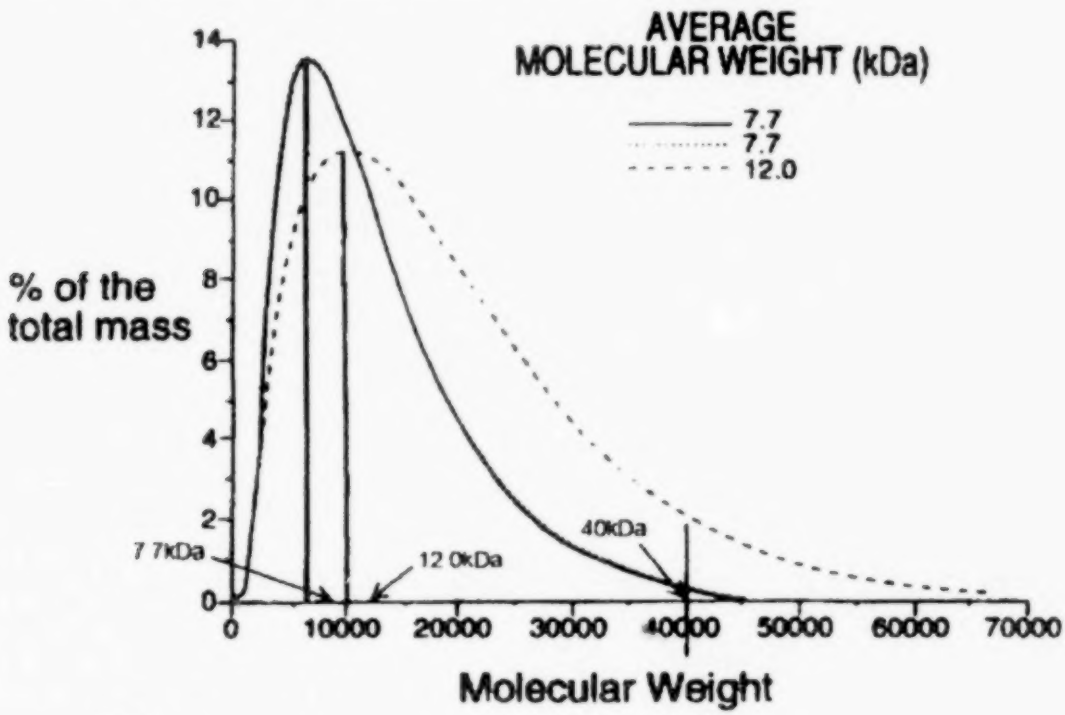

FIG. 1

Pet. App. 11a.

Because the patents and their prosecution history provided no indication as to which type of molecular weight Teva claimed, the court of appeals held indefinite and invalid the Group I claims, which include the only claim with a September 1, 2015 expiration date. The court of appeals went on, however, to affirm the validity and infringement of other ("Group II") claims, which the court held did not depend on average molecular weight. All of the Group II claims expire on May 24, 2014. Accordingly, the injunction has now been modified so that Sandoz and Mylan are barred from marketing copolymer-1 until May 24, 2014.

Teva sought rehearing and rehearing en banc. In that petition, Teva argued for the first time that the standard of review for claim construction should be changed, requesting that the Federal Circuit hold this case pending its decision in *Lighting Ballast*, in which it already had ordered en banc review. In *Lighting Ballast*, the en banc court is considering whether it should overrule its decision in *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc), which held that claim construction is a question of law subject to de novo review, and should instead "afford deference to any aspect of a district court's claim construction" and "[i]f so, which aspects should be afforded deference." *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 500 F. App'x 951, 952 (Fed. Cir. 2013). The en banc Federal Circuit declined to hold this case pending *Lighting Ballast* and denied Teva's petition—without

dissent and without even calling for a response from Sandoz and Mylan.

Teva thereafter filed what it called a "motion to correct the judgment" (which repeated its rehearing petition arguments), as well as a motion to stay the mandate pending a certiorari petition. The Federal Circuit denied both motions, again without dissent or calling for a response.

3. Subsequent proceedings before the Patent Office

On August 12, 2013, Teva filed an application with the United States Patent and Trademark Office (Patent Office) asking that it reissue the '808 patent to correct the error in the claim language identified by the Federal Circuit. *See* Appl. No. 13/964,856, http://portal.uspto.gov/pair/PublicPair (search by application number). Reissue of patents to correct an error requires an oath by the applicant admitting the existence of the error to be corrected. 35 U.S.C. § 251; 37 C.F.R. §§ 1.63, 1.175; Manual of Patent Examining Procedure §§ 1402, 1414. The reissue application remains pending before the Patent Office.

4. Prior proceedings before this Court

Arguing that it faced imminent irreparable harm and that the question presented in its petition urgently required this Court's review, Teva asked the Chief Justice to recall and stay the mandate of the Federal Circuit. Appl. to Recall and Stay Mandate, *Teva Pharm. USA, Inc. v. Sandoz Inc.*, No. 13A458

(U.S. Nov. 4, 2013). The Chief Justice denied Teva's application. Teva then waited to file its petition until the ninetieth day after denial of rehearing.

ARGUMENT

A. Teva's Question Presented Does Not Warrant This Court's Review

Teva makes an extraordinary request: it seeks immediate review of the Federal Circuit's 16-year-old decision in *Cybor*, even though the en banc Circuit currently is reconsidering *Cybor*. There is no need for this Court's review.

1. Certiorari is not needed to review the correctness of the Federal Circuit's Cybor *decision*

Teva asserts that certiorari is warranted to review whether the Federal Circuit's decision in *Cybor*, which held that all aspects of claim construction are reviewed de novo on appeal, is consistent with Rule 52(a) of the Federal Rules of Civil Procedure. Pet. 3, 21-23. Teva describes what it considers to be an internal division within the Circuit, contending that "a majority of the Federal Circuit" has continued to insist that all aspects of claim construction are reviewed de novo, even in the face of a "growing number of Federal Circuit judges [who] have concluded that the standard of review their court applies is flawed or simply wrong." Pet. 3.

But any internal division concerning the continued validity of *Cybor* soon will be addressed by the

full Federal Circuit itself. In *Lighting Ballast*, the en banc Federal Circuit already is reconsidering whether and to what extent a district court's claim-construction ruling is entitled to deference on appeal. And "[i]t is primarily the task of a Court of Appeals to reconcile its internal difficulties." *Wisniewski v. United States*, 353 U.S. 901, 902 (1957).

Circumstances thus have changed significantly since two Terms ago when, Teva says, this "Court might well have taken up this question" in *Retractable Technologies, Inc. v. Becton, Dickinson & Co.*, No. 11-1154 (cert. denied Jan. 7, 2013). Pet. 27. While the petitioner there urged that this Court's review was needed because the Federal Circuit had "steadfastly refused to reconsider its decision in *Cybor*," that is no longer the case. Pet. for Writ of Cert. at 3, *Retractable Techs.*, *supra*. The en banc Circuit is expressly considering whether to "overrule *Cybor*" in whole or in part. *Lighting Ballast*, 500 F. App'x at 951. Moreover, when the Solicitor General suggested in *Retractable Technologies* that the standard-of-appellate-review issue might warrant this Court's review in some future case, that suggestion was based on his view of *Cybor*. U.S. Amicus Br. at 19-21, *Retractable Techs.*, *supra*; *contra* Pet. 23. But that view is now being considered by the en banc Federal Circuit, where the United States has both filed an amicus brief and presented oral argument.

With *Lighting Ballast* fully briefed, argued, and under submission to the full Federal Circuit, the issue posed by Teva is not worthy of this Court's

review. This Court recently has refused to review the same question presented. *See, e.g.*, *Saffran v. Johnson & Johnson*, No. 13-405 (cert. denied Jan. 27, 2014). There is no reason for a different result here.

2. *There is no reason to presume that this Court's review will be needed regardless of the outcome of* Lighting Ballast

Teva contends that this Court's immediate review is needed despite the pendency of *Lighting Ballast* and regardless of the outcome of the en banc court's review. More specifically, Teva argues that "a decision by today's Federal Circuit judges, no matter what it may be, cannot provide a sure and certain answer to this question" and each time the Circuit has attempted to clarify the law, "the dissenters have vowed to keep up the fight." Pet. 28-29.

But there is no reason to presume that this Court's intervention will be needed no matter how the en banc Federal Circuit resolves the issue. This Court does not review every en banc decision from that Circuit, or any other. And it would be an affront to the Federal Circuit to preempt the en banc court's consideration by granting review here. This is not a case in which a "sole outlier court of appeals had already granted rehearing en banc whether to overrule its precedent and eliminate the circuit split." Pet. 28 n.10. It is a case where there is no circuit conflict and the court of appeals with exclusive jurisdiction is reconsidering its position en banc based on extensive briefing and argument.

Nor is there reason to assume that *Lighting Ballast* will not resolve any intra-circuit division concerning *Cybor*. The changed composition of the Federal Circuit, which Teva identifies as a reason for granting review, actually cautions against review. *Contra* Pet. 29-30. Only three members of the Federal Circuit who decided *Cybor* (and just one in the majority) are participating in the en banc review in *Lighting Ballast*. *See Cybor*, 138 F.3d 1448. If anything, the Circuit's new membership is reason to allow that court, which reviews hundreds of claim-construction rulings each year, to resolve *Lighting Ballast*—and to allow the rule of *Lighting Ballast* to percolate in future cases before this Court decides whether to step in. *See* Pet. 31 (noting that the Circuit decides "dozens" of claim-construction cases each month).

Teva speculates that the Circuit is unlikely to revisit *Cybor* because it did not reach the question in *Phillips*. Pet. 5-6, 28. But in *Phillips* the en banc court was faced with multiple issues, and it resolved the case by establishing the substantive framework used to construe a patent's claims. *Phillips v. AWH Corp.*, 376 F.3d 1382, 1383 (Fed. Cir. 2004) (ordering rehearing en banc and identifying issues for en banc briefing and review); *Phillips*, 415 F.3d at 1312 ("The principal question that this case presents to us is the extent to which we should resort to and rely on a patent's specification in seeking to ascertain the proper scope of its claims."). Unlike *Phillips*, the only issue before the en banc court in *Lighting Ballast* is

whether *Cybor* should be overruled and the level of deference, if any, that should be afforded a district court's claim construction. *Lighting Ballast*, 500 F. App'x at 951-952.

Finally, Teva demonstrates no urgent need for this Court's review. Teva's own actions belie any such claim: it chose not to file its petition in time for it to be heard on the merits this Term. *Cybor* has been the rule for 16 years. If *Lighting Ballast* announces a rule of law warranting this Court's consideration, the Court can grant review in that case—or in one of the other innumerable claim-construction cases that will apply it.

B. This Case Is An Unsuitable Vehicle To Consider The Appellate Standard Of Review

1. Lighting Ballast, or a case applying its rule, would be a better vehicle to review the question presented

If this Court wishes to consider the standard of appellate review for claim-construction rulings, *Lighting Ballast*, or a case applying the rule of *Lighting Ballast*, would be the appropriate vehicle to do so. *Contra* Pet. 29-31. The Federal Circuit's en banc decision will explore fully what deference, if any, should be accorded to which aspects of a district court's claim-construction ruling. A petition following *Lighting Ballast* would permit this Court to review the considered views of the en banc Federal Circuit and any percolation of those views that has occurred since that decision. This Court may then consider whether

review is warranted in a case in which, unlike this one, the court of appeals has addressed the application of the rule of *Lighting Ballast* to the facts presented.

By contrast, this case is not a suitable vehicle. The Federal Circuit's decision here contains *no* discussion of what should be the standard of appellate review for claim-construction rulings. Indeed, Teva did not argue that the standard of review for claim construction should be changed (or even raise Rule 52) until its petition for rehearing. As such, nothing about this case makes it a more suitable vehicle than *Lighting Ballast* (or a case following *Lighting Ballast*).

2. *The standard of review made no difference in the outcome of this case*

In fact, this is a particularly unsuitable vehicle because the court of appeals correctly held a subset of the claims at issue invalid for indefiniteness, and that outcome would be the same regardless of the standard of review.

Teva conceded below that the patent claims at issue were ambiguous on their face because they did not specify which type of molecular weight was claimed. Pet. App. 8a ("It is undisputed that Group I claims contain an ambiguity because their plain language does not indicate which average molecular weight measure is intended."). On appeal, the court of appeals looked solely to the patent instruments

themselves and their prosecution history to hold the terms indefinite. Pet. App. 8a-10a.

First, the court observed that, during prosecution of these related patents before the Patent Office, Teva gave two flatly contradictory definitions of "average molecular weight." Pet. App. 9a. As discussed above, while prosecuting one patent, Teva informed the Patent Office that one of ordinary skill in the art would understand "average molecular weight" to mean "peak" molecular weight. Pet. App. 9a (quoting C.A. JA3258). Yet in prosecuting another, Teva told the Patent Office that "average molecular weight" meant "weight average molecular weight." Pet. App. 9a (quoting C.A. JA3229). No matter what an expert might later say in litigation, "Teva's two definitions cannot be reconciled." Pet. App. 9a.

Second, the court of appeals looked to the common specification of the asserted patents and determined that it too provided no guidance regarding the meaning of "average molecular weight." Pet. App. 9a-10a. The court recognized that Figure 1 of the patent contradicted the declaration of Teva's expert that the figure referred to "peak" molecular weight. Pet. App. 9a-10a. Even a cursory examination of the patent instrument demonstrated that "the peaks of the curves in Figure 1 do not correspond to the values denoted as 'average molecular weight' in the figure's legend." Pet. App. 10a. Indeed, those reported "average molecular weight" values were closer to "weight average molecular weight" than to "peak" molecular

weight—as even Teva's expert admitted. Pet. App. 10a; *see* C.A. JA5824-5825.

Simply put, the court of appeals properly refused to allow a litigation expert to determine the ultimate meaning of the patent instruments. That outcome would not change under any standard of review.[1]

3. *The nature of the extrinsic "evidence" in this case makes this a poor vehicle to explore the contours of any deference*

Given the square contradiction between the intrinsic record and Teva's expert's declarations, this is an especially poor vehicle for considering what deference, if any, should be accorded to a district court's claim-construction rulings under Rule 52, and what the contours of any such deference should be.

The expert "testimony" Teva cites consisted solely of written declarations of its paid expert. *See* Pet. 9, 14, 25. The purported "facts" on which Teva relies were its expert's litigation-driven "interpretation" of the asserted patents themselves and their prosecution history. *See* C.A. JA1016-1018, JA7097-7101 (Grant declarations discussing "average molecular weight"). Contrary to Teva's assertion, these were not declarations about "the *historical* meaning of a claim term to one of ordinary skill in the art at the time of

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[1] Indeed, in its pending reissue application to the Patent Office, Teva has conceded that the '808 patent claim as written is erroneous.

the invention." Pet. 23 (quoting U.S. En Banc Amicus Br. at 15, *Lighting Ballast*, *supra*) (emphasis added). Nowhere did these expert declarations contend that "average molecular weight" had an established meaning at the time of the invention. In fact, Teva admitted that the term was ambiguous and had no fixed meaning. Pet. App. 8a.

As such, the "evidence" Teva cites is not the kind of "historical fact" evidence that the United States has contended could support findings warranting deference on appeal. *Contra* Pet. 23. Quite the opposite: the United States has explained that courts "must exercise care to distinguish relevant and probative expert testimony (e.g., testimony about the accepted meaning of a claim term in the relevant art at the time of the invention) from irrelevant opinion (e.g., an expert's present, subjective understanding of a patent claim)." U.S. En Banc Amicus Br. at 20, *Lighting Ballast*, *supra*; *see Phillips*, 415 F.3d at 1318. Teva's expert declarations offered only the latter.

More significantly, the court of appeals properly refused to defer to the district court's decision to "credit" Teva's expert's declarations that directly contradicted what the legal documents actually said. Where the patents and their prosecution history did not support his argument, Grant simply opined that those documents—the public record of the asserted invention—were wrong. For example, as to one of the two irreconcilable definitions of "average molecular weight" in the prosecution history, Grant contradicted

the public record by saying that one of skill in the art reading the prosecution history "would have understood that to be a misstatement." C.A. JA7100. Moreover, because Grant's readings of the "peaks" in Figure 1 of the specification did not correspond to the "average molecular weight" values denoted in that figure's legend, Grant opined that Figure 1 was in error and that his calculation fell within an unspecified "margin of error." C.A. JA3115-3116.

This cavalier contradiction of the intrinsic record did not merit consideration in claim construction, much less deference on appeal. *See U.S. Indus. Chems., Inc. v. Carbide & Carbon Chems. Corp.*, 315 U.S. 668, 678 (1942) ("It is inadmissible to enlarge the scope of the original patent by recourse to expert testimony * * * "). Indeed, in *Phillips*, the en banc Federal Circuit instructed that courts "should discount any expert testimony that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent." *Phillips*, 415 F.3d at 1318 (internal quotation marks omitted). The court of appeals explained that "conclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court." *Ibid.* And it is the job of neither an expert nor the district court to correct "misstatements" in the intrinsic record to preserve patent validity. *Ibid.*

Teva does not challenge *Phillips*' elevation of the intrinsic patent record above the extrinsic evidence of

expert testimony, and that elevation fully comports with this Court's precedent. Yet for Teva to prevail, this Court would need to set aside that well-settled framework. That is further reason to deny review here, as those unchallenged claim-construction principles could preclude the Court from even reaching the question presented.

For similar reasons, Teva is wrong in suggesting that certain amici in *Lighting Ballast* advocate Teva's approach. Pet. 23 & n.8. None of those associations has argued that extrinsic expert testimony should trump a patent record that it squarely contradicts. *See* ABA En Banc Amicus Br. at Add. 1, *Lighting Ballast*, *supra* (ABA resolution advocating that expert testimony may not be used to contradict a patent's intrinsic record); AIPLA En Banc Amicus Br. at 14, *Lighting Ballast*, *supra* ("Where, for example, the district court determines a factual issue based on expert testimony, this Court must 'discount [such] expert testimony "[if] that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history * * * "'") (quoting *Phillips*, 415 F.3d at 1318); FCBA En Banc Amicus Br. at 10-11, *Lighting Ballast*, *supra* (explaining that no deference is due to extrinsic evidence that contradicts the intrinsic evidence or that does not inform questions of historical fact).

In short, regardless of the standard of review, there were no factual findings here that warranted deference. At the very least, the square contradiction between the intrinsic record and the expert's

declarations make this a poor vehicle to assess which, if any, factual findings relating to claim construction should receive deference on appeal.[2]

4. *The court of appeals' actions confirm that a different standard of review would not change the outcome*

The court of appeals' repeated rebuffs of Teva's attempts to have this case stayed pending *Lighting Ballast* further demonstrate that the standard of review was not outcome determinative.

The panel issued its unanimous decision in this case while *Lighting Ballast* was pending before the en banc court. The entire court of appeals then denied Teva's rehearing petition (which was based primarily on *Lighting Ballast*), declined to hold the case for *Lighting Ballast*, and refused Teva's plea to stay issuance of the mandate pending the outcome in *Lighting Ballast*. *See* Pet. App. 84a, 87a. Those repeated rejections demonstrate that the court of appeals did not deem the standard of review dispositive of the

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[2] *Great Northern Railway Co. v. Merchants' Elevator Co.*, 259 U.S. 285, 291-292 (1922), does not help Teva's cause. *Contra* Pet. 19-20. There, this Court simply affirmed the general rule that construction of tariffs "presents ordinarily a question of law which does not differ in character from those presented when the construction of any other document is in dispute." *Great Northern Railway*, 259 U.S. at 291. Although the Court observed that an issue of fact might arise where resort to extrinsic evidence was necessary for construction, *id.* at 292, the Court did not address whether deference could be afforded to an expert's reading of the legal instrument itself.

outcome here. Given that the same legal question is pending before the en banc court, that court's assessment warrants this Court's deference.

Respect for the court of appeals' assessment is particularly appropriate here, as the Federal Circuit judges on the panel in this case were Chief Judge Rader and Judge Moore, two of the most vocal judges calling for a deferential standard of review of claim-construction rulings. *See, e.g.*, *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 659 F.3d 1369, 1373 (Fed. Cir. 2011) (Moore, J., and Rader, C.J., dissenting from denial of rehearing en banc); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1040-1041 (Fed. Cir. 2006) (Michel, C.J., and Rader, J., dissenting from denial of rehearing en banc); *id.* at 1044-1045 (Rader, J., dissenting from denial of rehearing en banc); *id.* at 1045-1046 (Moore, J., dissenting from denial of rehearing en banc). Indeed, Teva prominently relies on opinions by those two judges. Pet. 3 n.2, 5, 21. Nevertheless, Judge Moore authored, and Chief Judge Rader joined, the decision holding a subset of the claims indefinite and then repeatedly declined to hold this case for *Lighting Ballast*. That further confirms that the standard of review did not affect the outcome here.

C. There Is No Reason To Hold The Petition

In the alternative, Teva suggests (Pet. 32-35) that the Court hold its petition pending the resolution of *Nautilus, Inc. v. Biosig Instruments, Inc.*, No. 13-369 (cert. granted Jan. 10, 2014). But Teva's question

presented does not invoke the questions presented in *Nautilus*, and that alone should preclude Teva from obtaining any relief under that decision. In any event, because the result in *Nautilus* should not affect the disposition of this case, there is no reason to hold the petition.

In *Nautilus*, this Court is considering the standard for declaring a patent indefinite under 35 U.S.C. § 112(b), which requires that a patent contain "one or more claims particularly pointing out and distinctly claiming the subject matter which the [applicant] regards as the invention." Under Federal Circuit precedent, a patent is not indefinite as long as it is "amenable to construction, however difficult that task may be," even if "the conclusion may be one over which reasonable persons will disagree." *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001). Under that standard, a court may invalidate a claim for indefiniteness only if the claim is "insolubly ambiguous, and no narrowing construction can properly be adopted." *Ibid.*

According to Teva, the parties to *Nautilus* are "likely to argue" that case "in a way highly relevant to this case." Pet. 32. But neither the questions presented nor any of the petition-stage briefs in *Nautilus* mentions the standard of appellate review of indefiniteness determinations. Instead, the parties have focused on the underlying substantive issue of what standard of indefiniteness should be applied, in the first instance, to determine the validity of a patent claim. That issue is not relevant to the question

presented as framed by Teva, which concerns only the *appellate* standard of review. Thus, regardless of the outcome of *Nautilus*, Teva should not be entitled to any relief under that decision. *Yee v. City of Escondido*, 503 U.S. 519, 535 (1992) ("The framing of the question presented has significant consequences, however, because under this Court's Rule 14.1(a), '[o]nly the questions set forth in the petition, or fairly included therein, will be considered by the Court.'"). That alone is sufficient reason not to hold the petition.

Moreover, the issues in *Nautilus* are not relevant to this case in any way that could possibly help Teva. The petitioner in *Nautilus* has argued that the Federal Circuit's substantive indefiniteness standard makes it too difficult to establish indefiniteness and that the Federal Circuit is wrongly upholding ambiguous patent claims. Pet. for Writ of Cert. at 2-5, *Nautilus*, *supra*. The respondent, by contrast, has argued that the Federal Circuit's substantive indefiniteness standard is correct. Br. in Opp. at 26-28, *Nautilus*, *supra*. Neither party, however, has suggested that this Court should adopt a substantive indefiniteness standard that is *more* favorable to patentees. Indeed, it is difficult to see how *any* standard could be more deferential than that currently applied by the Federal Circuit, which upholds patent claims as long as they are not "insolubly ambiguous" and thus incapable of construction. *Exxon Research*, 265 F.3d at 1375; *accord Enzo Biochem, Inc. v. Applera Corp.*, 605 F.3d 1347, 1348 (Fed. Cir. 2010) (Plager, J.,

dissenting from denial of panel rehearing) ("[T]he general conclusion from our law seems to be this: if a person of ordinary skill in the art can come up with a plausible meaning for a disputed claim term in a patent, that term, and therefore the claim, is not indefinite.").

Here, applying that "insolubly ambiguous" test, the Federal Circuit held that a subset of the patent claims at issue were invalid for indefiniteness. Pet. App. 6a-11a. Because Teva's claims could not survive under the current indefiniteness standard, they will, *a fortiori*, be unable to survive under any more rigorous standard this Court might adopt in *Nautilus*. That is yet another reason not to hold the petition.

In a last-ditch effort to delay final resolution of this case, Teva asks in a footnote that its petition also be held pending the disposition of *Highmark Inc. v. Allcare Health Management Systems, Inc.*, No. 12-1163, and *Octane Fitness, LLC v. Icon Health & Fitness, Inc.*, No. 12-1184 (both to be argued Feb. 26, 2014). Pet. 34 n.18. But those cases involve the standards that trial and appellate courts should apply in determining whether a case is "exceptional" and warrants an award of attorney's fees under 35 U.S.C. § 285. Those cases have no relevance here, where no award of attorney's fees is at issue.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted,

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FEBRUARY 5, 2014

REPLY BRIEF

No. 13-854

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Petition for a Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

REPLY BRIEF FOR PETITIONERS

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RULE 29.6 STATEMENT

The Rule 29.6 statement included in the petition for a writ of certiorari remains accurate.

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REPLY BRIEF FOR PETITIONERS

The Federal Circuit overturned the district court's factual findings about matters of historical fact without deciding or even considering whether those findings were clearly erroneous. The Federal Circuit once again acted on the notion that every aspect of claim construction is a question of law to be reviewed "*de novo*," Pet. App. 7a, 10a, a position erroneously said to be compelled by this Court's decision in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996). *See Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1455-56 (Fed. Cir. 1998).

That rule is ripe for reconsideration. This Court must examine it, because the Federal Circuit will not abandon it. On February 23, 2014, the Federal Circuit decided *Lighting Ballast Control LLC v. Philips Electronics North America*, the case that respondents urged this Court to await. In a closely-divided *en banc* opinion, the Federal Circuit, made it clear that it would continue to apply that rule as a matter of *stare decisis*. *See* App., *infra*, 1a-95a.

Respondents offer *not a single word* in defense of that rule on the merits. Rather, they urge this Court to grant review, if at all, only in *Lighting Ballast* or some subsequent case—once the decision in this case is safely final. But there is no reason to wait. Now that the Federal Circuit has decided *Lighting Ballast*, this Court has the benefit of that court's views, and of the dissenters'. Nothing about *Lighting Ballast* turned on the facts, and nothing makes it a superior vehicle to any other case. There is therefore no reason to wait for a petition in *Lighting Ballast* that may never come. As the Solicitor General pre-

viously advised the Court, the Federal Circuit's rule is wrong and this Court should review it in an appropriate case. Pet. 22-23, 27. This is such a case, and the Court should not pass it up.

Respondents maintain that they would still win *if* the Federal Circuit applied a clear-error standard of review. That speculation is unfounded and ignores the district court's sound, substantially unrebutted fact-finding.

Furthermore, the very question here—is claim construction a question of law or fact?—lies at the heart of *Nautilus, Inc. v. Biosig Instruments, Inc.*, No. 13-369, a case to be argued in this Court in April. In that case or this one, this Court should provide an answer.

I. This case is a proper vehicle because the proper standard of review is outcome-determinative.

Respondents insist that the standard of review made no difference in this case. They rely heavily (Opp. 2, 25-26) on the Federal Circuit's unexplained denial of rehearing, but nothing in that one-line order indicates that the panel reconsidered the case under clear-error review. On the contrary, it is now clear that the court denied rehearing and issued the mandate because it knew the *en banc* court had voted to reaffirm *Cybor*, making it pointless to hold this case in the Federal Circuit any longer.

Respondents also contend that the panel's view of the evidence was correct. And they seek to justify overturning the district court's contrary findings by insisting that the case does not turn on "'historical fact' evidence." *E.g.*, Opp. 22.

But respondents entirely miss the point. To demonstrate that applying the correct standard of review would not affect the outcome, respondents would have to show that the district court's findings in support of claim construction were "clearly erroneous." They do not even try to make *that* argument. Nor could they: a district court's findings are not clearly erroneous merely because the reviewing court would find the facts differently. *E.g.*, *Anderson v. City of Bessemer City*, 470 U.S. 564, 573 (1985). Indeed, respondents do not even *acknowledge* the district court's findings, understandably preferring the contrary "findings" made by the Federal Circuit on its *de novo* review of the record. They certainly do not refute or even address the substantial evidence supporting the district court's findings. *See* Pet. 24-26.

Respondents are simply incorrect in asserting that Dr. Grant offered only his own subjective understanding and that the district court's findings therefore should be disregarded. *E.g.*, Opp. 21-22. For example, the panel placed crucial reliance on Figure 1 of the patent specification (as annotated in red by respondents' counsel), Opp. 11, Pet. App. 10a-11a; respondents assert that a "cursory examination" of that figure was enough to undermine the district court's claim construction. Opp. 20-21, 23. But Dr. Grant—who had far better than a "cursory" understanding of the relevant science—specifically addressed that very argument and explained why, given the data conversions needed to produce Figure 1, M_p would not necessarily appear at the peak of that figure. Pet. App. 118a, 126a-27a. Dr. Grant did not contradict the patent; he explained the science that it taught. Dr. Grant's evidence on that scientific, fac-

tual issue was unrebutted, and the district court properly credited it. *Id.* at 49a. The panel needed a highly compelling reason to set aside the finding. It gave *no* reason, and respondents give none here.

Respondents' complaint that Dr. Grant gave no "live testimony" (Opp. 2, 9) is a red herring. There was no live testimony in *Lighting Ballast* either. Pet. 27 & n.9. That fact does not eliminate the need for deference, in either case. Pet. 26-27. And in any event, respondents cross-examined Dr. Grant and submitted that testimony during the summary-judgment proceedings. They could have called him, or their own expert, to testify at trial if they had wished. They simply had no evidence to counter Dr. Grant's explanation.

If the Federal Circuit had credited the district court's findings, it would have been required to reject the indefiniteness defense. Despite respondents' attempt to create ambiguity using the prosecution history, *see* Opp. 20, 22-23, those materials are "less useful" in claim construction than the patent specification itself, which is the "best" and "primary basis for construing the claims." *Philips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (*en banc*) (citations omitted). And the district court's findings leave no doubt that a person of ordinary skill in the art, reading the specification, would have discerned the meaning of average molecular weight.

Changing the standard of review thus would change the outcome.[1] The panel gave no indication

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[1] Even if that were not so, this Court has reviewed unsettled standard-of-review issues even where the answer ultimately did not affect the outcome of the particular case. *See, e.g., Russell*

that it considered the district court's findings clearly erroneous; to the contrary, the panel made clear that it reviewed *de novo* in making findings inconsistent with those of the district court. Pet. App. 7a, 10a.[2]

Under the standard of review this Court has specified in Fed. R. Civ. P 52(a)(6), the substantial evidence—indeed, one-sided evidence—supporting the district court's findings should have led to affirmance. This case therefore squarely presents the question of what the proper standard of review should be.[3]

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v. Salve Regina Coll., 938 F.3d 315, 315-16 (1st Cir. 1991) (reaching same result after this Court reversed on standard-of-review issue).

[2] Respondents' other vehicle argument—that Teva did not ask the panel to apply clear-error review, Opp, 2, 12, 19—is both factually wrong, *see* Teva C.A. Br. 26, and legally irrelevant. The panel could not have overruled *Cybor*, and the *en banc* court has now declined to do so in any event.

[3] The "concession" to which respondents allude (Opp. 21 n.1) refers to a submission to the Patent Office seeking reissuance of the patent. Teva made that submission following the Federal Circuit's decision and, on February 13, 2014, updated its submission with the required oath acknowledging that an "error" has caused the patent to be "inoperative or invalid," 37 C.F.R. § 1.175(a). The Patent Office is still considering Teva's reissue application, however, and indeed, respondents have vigorously and repeatedly urged the Patent Office not to reissue the patent, relying in part on arguments that have nothing to do with the issues addressed by the Federal Circuit.

II. This Court should not deny the petition in anticipation of a petition in *Lighting Ballast*, because that case may never reach this court and this case is a suitable vehicle for resolving the issue.

Even though this case squarely presents the standard-of-review question, respondents insist that *only Lighting Ballast*, or a later one, can be a proper vehicle. While convenient for respondents, that notion is not based on this Court's certiorari criteria. Nor is it based on anything making *Lighting Ballast* a superior vehicle. *See* Pet. 27 & n.9. Indeed, the *en banc* opinions in *Lighting Ballast* do not even discuss the facts of that case. Nothing about *Lighting Ballast* makes it a uniquely suitable vehicle. The Court can read the *en banc* opinions for itself, whether it grants review in this case or any other case. And waiting for a petition in *Lighting Ballast* specifically may be in vain because the losing patentee may not seek certiorari. *See* Pet. 31.[4]

Furthermore, because Federal Circuit decided in *Lighting Ballast* to continue to follow *Cybor* irrespective of its merits and notwithstanding its flaws, there is a compelling need for review by this Court without further delay. A bare majority of the Federal Circuit has declined to change its collective mind after a fourth *en banc*, despite changes in membership (Opp. 17) and a barrage of criticism from everyone ranging

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[4] Respondents incorrectly assert (Opp. 16) that the Court has denied certiorari in a similar posture. That is incorrect—the *Saffran* case would not have been a suitable vehicle because the district court made no factual findings, and in any event, the posture has changed now that the Federal Circuit has reaffirmed the rule Teva challenges.

from the United States to its own former Chief Judge. Respondents' plea for further "percolat[ion]" (Opp. 17, 18) is absurd: the Federal Circuit has declared that it will simply continue to brew exactly the same bitter product that it has brewed for well over a decade.

Indeed, the concurring and dissenting opinions in *Lighting Ballast*, confirm Teva's argument that the answer to the question presented turns on what this Court meant in *Markman*. Although the *Lighting Ballast* majority relied on principles of *stare decisis*, Judge Lourie's concurrence defended the *Cybor* rule on the merits primarily as a logical consequence of this Court's ruling in *Markman* that claim construction was a matter for the trial court, and not a jury, in the first instance. By contrast, Judge O'Malley's dissent for herself and three colleagues concluded upon a close analysis that *Markman* did not compel *de novo* review but instead "repeatedly acknowledged the factual component of claim construction." App., *infra*, at 51a. Only this Court can resolve which of these conflicting views of *Markman* is correct.

The *Lighting Ballast* majority, which included the author of the decision below and other judges who had previously criticized the *Cybor* rule, tacitly acknowledged this point. By basing the decision to uphold the *Cybor* rule on *stare decisis* grounds without even attempting to resolve the issue on the merits, a majority of the Federal Circuit essentially threw up its hands, despairing that it could reach consensus on the meaning of *Markman* and the proper standard of review. The message is clear: only this Court, which is decidedly *not* bound by Feder-

al Circuit precedent (especially incorrect precedent), can definitively resolve the issue.

The standard of review plainly is "an important question of federal law that has not been, but should be"—and can only be—settled by this Court." Sup. Ct. R. 10(c).

III. Because there is a reasonable likelihood that resolution of the issues accepted for review in *Nautilus* will determine what standard of review applies to claim construction, this Court may wish to hold the petition in this case pending its decision in *Nautilus*.

The Court already has granted review in *Nautilus*, to review questions that will require this Court to decide whether "claim construction is purely legal," as the Federal Circuit held in *Cybor*, 138 F.3d at 1456, or may turn on underlying factual issues, as Teva contends. If this Court holds in *Nautilus* that claim construction is not a pure question of law, the basic premise of the Federal Circuit's rule of *de novo* review would be fatally undermined. *See* Pet. 32-35. That is more than sufficient to justify holding Teva's petition until *Nautilus* is decided and, depending on the outcome, may justify directing the Federal Circuit to reconsider this case in light of *Nautilus*. In arguing against a hold, respondents simply ignore the specific questions presented in *Nautilus* and their relevance to this case.

The defense of indefiniteness under 35 U.S.C. § 112, at issue in *Nautilus*, invariably turns on the meaning of patent claims and whether that meaning is expressed clearly enough. In *Nautilus*, the Feder-

al Circuit upheld patents against an indefiniteness challenge, because they contained sufficient information to allow a person of ordinary skill in the art to discern the boundaries of the relevant claim term and, therefore, the claims were not "insolubly ambiguous."

This Court granted review on both questions presented by the *Nautilus* petition. The first concerns whether the Federal Circuit's standard for indefiniteness accurately implements the requirement of § 112 that claims be "distinct." The second question is whether "the presumption of validity dilute[s]" that requirement. Pet. for Cert. at i, *Nautilus, supra*.

The second question arose because the Federal Circuit deemed the statutory presumption of validity, 35 U.S.C. § 282(a), to inform the standard of indefiniteness. The standard allows some degree of ambiguity, so long as the patent claim's meaning can be discerned using the traditional canons of claim construction. *See Biosig Instruments, Inc. v. Nautilus, Inc.*, 715 F.3d 891, 902 (Fed. Cir. 2013) (*Nautilus* Pet. App. at 14a, 21a-22a). Thus, this Court will consider the nature of the presumption of validity and its relevance in determining the meaning of a patent claim that is challenged for indefiniteness.

But the presumption of validity set out in Section 282(a) creates an "evidentiary standard of proof" that applies only to questions of *fact*. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2253 (2011) (Breyer, J., joined by Scalia and Alito, JJ., concurring). Accordingly, to determine how the presumption of validity affects the indefiniteness defense, this Court will have to address whether the claim-construction

issues on which indefiniteness turns are questions of fact (to which the presumption applies) or of law (as to which it is irrelevant). As Teva has described, the parties in *Nautilus* have already squared off on this point, with the petitioner insisting that the presumption of validity plays no role because "there are no factual determinations in claim construction," and the patentee arguing that claim construction involves fact questions and the presumption applies to those questions. Pet. 32-33. Both sides invoke this Court's decision in *Markman*, as do the concurring and dissenting opinions in *Lighting Ballast*.

Respondents insist that the questions presented in *Nautilus* do not mention "the standard of appellate review," Opp. 27-28, but that is a *non sequitur*. If this Court accepts the patentee's argument in *Nautilus* that claim construction is not "purely legal," that holding will undo the very premise on which the Federal Circuit has based its standard of appellate review. Such a decision by this Court would, at a minimum, be an "intervening development[] reveal[ing] a reasonable probability that the decision below rests upon a premise that the lower court would reject if given the opportunity for further consideration," and warranting a GVR. *Lawrence v. Chater*, 516 U.S. 163, 167 (1996) (per curiam).[5]

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[5] The test for GVRs is not, as respondents would have it, whether the questions presented in Teva's petition and Nautilus's are the same. Dozens of recent GVRs show that respondents' same-question-presented test is wrong. *See, e.g.*, *Giovanniello v. ALM Media, LLC*, 133 S. Ct. 159 (2012) (No. 11-1411) (GVRing petition presenting statute-of-limitations question in light of opinion on jurisdictional question). And the standard for a *hold* is not whether a GVR is certain, but whether it is reasonably likely.

Respondents also contend (Opp. 28-29) that the Court has only two options in *Nautilus*: ratify the Federal Circuit's current indefiniteness doctrine or make the test "more rigorous." The Court faces no such constraint: unlike the Federal Circuit, this Court need not (and should not) conform its holding to *Cybor*. In answering the presumption-of-validity question presented in *Nautilus*, therefore, this Court is free to give an answer that the Federal Circuit panel in *Nautilus* was not: that the presumption of validity sometimes applies to claim construction *because claim construction sometimes turns on factual issues*. And *that* holding would require the Federal Circuit to reconsider its rule reviewing findings on those factual issues *de novo*—the rule that allowed respondents to prevail on appeal. Crediting the district court's findings would defeat respondents' indefiniteness defense, under *any* indefiniteness standard.

Thus, this case and *Nautilus* share a common pivotal question: is claim construction purely legal? Given the substantial possibility that *Nautilus* will answer that question, or at least shed light on it, there is certainly no reason to follow respondents' urging and hurriedly deny the petition before *Nautilus* is even briefed, much less decided.

* * * * *

This case amply illustrates why this Court should bring to an end the Federal Circuit's practice of reviewing factual issues in claim construction *de novo*: the panel relied on its own "cursory" understanding (Opp. 20) of highly complex and technical scientific matters and concluded that because *the panel* could

not discern the meaning of the patent, neither could a skilled artisan. The district court's factual findings squarely refute that notion, and because those findings are not clearly erroneous, they should have been the end of the case. These facts starkly present the question that has long demanded an answer by this Court and that the Federal Circuit itself has given up trying to resolve on the merits. The Court should take this opportunity and resolve the matter.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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February 26, 2014

APPENDIX

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

LIGHTING BALLAST CONTROL LLC,
Plaintiff-Appellee,

v.

PHILIPS ELECTRONICS NORTH AMERICA CORPORATION,
Defendant,

AND

UNIVERSAL LIGHTING TECHNOLOGIES, INC.,
Defendant-Appellant.

2012-1014

Appeal from the United States District Court for the Northern District of Texas in case no. 09-CV-0029, Judge Reed O'Connor.

Decided: February 21, 2014

ANDREW J. DHUEY, of Berkeley, California, argued for plaintiff-appellee on rehearing en banc. With him on the brief were JONATHAN T. SUDER and DAVID A. SKEELS, Friedman, Suder & Cooke, of Fort Worth, Texas; and ROBERT P. GREENSPOON, Flachsbart & Greenspoon, LLC, of Chicago, Illinois.

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ON REHEARING EN BANC

Before RADER, *Chief Judge*, NEWMAN, DYK, PROST, MOORE, O'MALLEY, REYNA, WALLACH, and TARANTO, *Circuit Judges*.*

Opinion for the court filed by NEWMAN, *Circuit Judge*, with whom LOURIE, DYK, PROST, MOORE, and TARANTO, *Circuit Judges*, join.

Concurring opinion filed by LOURIE, *Circuit Judge*.

Dissenting opinion filed by O'MALLEY, *Circuit Judge*, with whom RADER, *Chief Judge*, and REYNA and WALLACH, *Circuit Judges*, join.

NEWMAN, *Circuit Judge*.

The court en banc granted the petition filed by patentee Lighting Ballast Control, in order to reconsider the holding in *Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc) establishing the standard of appellate review of district court decisions concerning the meaning and scope of patent claims—called "claim construction." Implementing the Supreme Court's decision in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996) (*Markman II*), *aff'g Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995) (en banc) (*Markman I*), this court in *Cybor* held that patent claim construction receives *de novo*

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* Circuit Judges Chen and Hughes took no part in the consideration or decision of the case.

determination on appeal, that is, review for correctness as a matter of law. Such review is conducted on the administrative record and any additional information in the record of the district court, and is determined without deference to the ruling of the district court.

In the case now before us, a panel of this court followed the *Cybor* standard and revised the district court's claim construction, applying *de novo* the statutory requirements of 35 U.S.C. §112 ¶16 and §112 ¶12.[1] Briefly, the panel held that the claim term "voltage source means" is a means-plus-function term requiring corresponding structure in the specification. On this claim construction, the panel reversed the district court and held the claims invalid for indefiniteness. The patentee requests rehearing, stating that on deferential appellate review the district court would not or should not have been reversed. This court undertook rehearing en banc for the purpose of reconsidering the standard of appellate review of claim construction.

For the reasons we shall discuss, we apply the principles of *stare decisis*, and confirm the *Cybor* standard of *de novo* review of claim construction, whereby the scope of the patent grant is reviewed as a matter of law. After fifteen years of experience with *Cybor*, we conclude that the court should retain plenary review of claim construction, thereby providing national uniformity, consistency, and

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[1] *Lighting Ballast Control, LLC v. Philips Electronics North America Corp.*, No. 7:09-CV-29-O, 2010 WL 4946343 (N.D. Tex. Dec. 2, 2010), *rev'd*, 498 Fed. App'x 986 (Fed. Cir. 2013), *withdrawn*, 500 Fed. App'x 951 (Fed. Cir. 2013).

finality to the meaning and scope of patent claims. The totality of experience has confirmed that *Cybor* is an effective implementation of *Markman II*, and that the criteria for departure from *stare decisis* are not met.

I

THE REHEARING ARGUMENTS

Lighting Ballast argues that *de novo* plenary determination of claim construction is improper appellate practice, stating that the interpretation of documents is fundamentally factual in nature, and that the district court's interpretation of patent claims requires deference on appeal. Lighting Ballast states that on deferential review the district court's claim construction for the patent in suit would be sustained, along with the ensuing judgment that the claims in suit are valid and infringed.

This en banc court agreed to reconsider the principle of *de novo* review of claim construction, and invited supplemental briefing and amicus curiae participation on the following questions:

(1) Should this court overrule *Cybor*?

(2) Should this court afford deference to any aspect of a district court's claim construction?

(3) If so, which aspects should be afforded deference?

The parties as well as the amici curiae were not of one mind, but divided among three general views, all

thoughtful and well presented.[2] The general positions are summarized:

The first view

The view favored by Lighting Ballast is that the *Cybor* decision is incorrect and should be entirely discarded. Lighting Ballast argues that this court in *Cybor* misapplied the Supreme Court's decision in *Markman II*, in that the Court had focused only on whether questions of patent claim construction are subject to jury trial, or whether this issue should be decided solely by a judge. These proponents state

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[2] Thirty-eight entities participated as amici curiae in twenty-one briefs. The participants are: Amazon.com, Inc.; American Bar Association; American Intellectual Property Law Association; Austin Intellectual Property Law Association; Association of the Bar of the City of New York; Association of University Technology Managers; Cisco Systems Inc.; Colorado State University Research Foundation; Connecticut Intellectual Property Law Association; Delaware Chapter of the Federal Bar Association; Dell Inc.; EMC Corporation; Federal Circuit Bar Association; Federation Internationale Des Conseils En Propriete Intellectuelle; Google Inc.; Hewlett-Packard Co.; Intel Corporation; the Intellectual Property Institute of William Mitchell College of Law; the Intellectual Property Law Association of Chicago; the Intellectual Property Owner's Association; former Chief Judge (ret.) Paul R. Michel; Professor Peter S. Menell; Microsoft Corp.; New-South Innovations; NUTech Ventures, Inc.; Patent Owners in the Lighting Industry; Public Patent Foundation; Red Hat, Inc.; San Diego Intellectual Property Law Association; SAP America Inc.; SAS Institute Inc.; Sigram Schindler Beteiligungs GmbH; the Science & Technology Corporation at the University of New Mexico (STC.UNM); the University of Nebraska Medical Center Technology Transfer Corporation (UNeMed Corp.); Wisconsin Alumni Research Foundation; TEC Edmonton; the University of Pittsburgh; the United States; and Yahoo! Inc. At the court's invitation, the United States participated in the argument.

that the Court in *Markman II*, in deciding the judge-jury question, did not change the traditional distinction between fact and law, recognized that there are factual aspects of claim construction, and did not address the standard of appellate review.

These proponents argue that the Court left intact the protocol of appellate deference to a district court's fact-based rulings, whether the facts relate to claim construction or any other issue, and whether the ruling is by a judge or by a jury. They state that the *Cybor* standard of plenary appellate review is incorrect, and remind us that the Court in *Markman II* described claim construction as a "mongrel practice" of law and fact with "evidentiary underpinnings," 517 U.S. at 378, 390. They argue that although the Court stated that "the interpretation of a so-called patent claim is a matter of law reserved entirely for the court," *id.* at 372, the Court did not strip claim construction of its essentially factual nature.

These proponents point out that in construing patent claims, expert testimony and documentary evidence may be presented to the district court. They argue that restoration of deferential appellate review on the clear error standard would not only respect the traditional trial/appellate relationship, but also is more likely to give weight to aspects involving credibility of witnesses. They point out that Federal Rule of Civil Procedure 52(a)(6) requires that the district court's factual findings receive review on the deferential clearly erroneous

standard,[3] citing *Pullman-Standard v. Swint*, 456 U.S. 273, 287 (1982) for its statement that Rule 52(a) "does not divide findings of fact into those that deal with 'ultimate' and those that deal with 'subsidiary' facts."

These proponents argue that patent claim construction is most reasonably classified as a question of fact, and that the Court's *Markman II* description of claim construction as better suited to determination by a judge rather than a jury does not affect the requirement of appellate deference to findings of fact made at the trial level. Thus Lighting Ballast urges that the *Cybor* standard of *de novo* review is incorrect and should be entirely discarded.

The second view

The second approach, favored by some amici curiae including the United States, may be viewed as a fusion or hybrid of *de novo* review and deferential review. These proponents acknowledge that the Court in *Markman II* described patents as "legal instruments" and stated that interpretation of patent claims is a "purely legal" matter, 517 U.S. at 391, but argue that the correct appellate approach is for the factual aspects of claim construction to be reviewed on the clearly erroneous standard, while the final conclusion receives review as a matter of law. *See, e.g.*, Brief of Amicus Curiae United States at 4

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[3] 3 Rule 52 (a)(6) *Setting Aside the Findings.* Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility.

("Because *Cybor* fails to acknowledge that claim construction may involve factual findings entitled to deferential review under Rule 52(a), it should be overruled. But this Court should reaffirm that the ultimate construction of a patent claim is a legal conclusion subject to *de novo* review."). The United States draws analogy to the ruling in the regulatory tariff case of *Great Northern Railway Co. v. Merchants' Elevator Co.*, 259 U.S. 285, 292 (1922), that when ambiguity arises in the construction of certain legal instruments, the ambiguity is resolved as a question of fact.

Some of these amici recognize that difficulties may arise in practice, in knowing which aspects of the district court's claim construction are subject to deferential review and which aspects receive *de novo* determination. They suggest a solution whereby the standard of review would depend on whether the district court's claim construction drew solely from the record of the patent and its prosecution history (called "intrinsic evidence"), or whether external information or witness testimony was presented in the district court (that is, "extrinsic evidence"). Applying this distinction, some amici propose that claim constructions based on extrinsic evidence would receive clearly erroneous review, for such evidence may entail credibility or reliability findings, while constructions based solely on the patent document and prosecution history would receive *de novo* review.

The proponents of a hybrid form of appellate review argue that this approach comports with the Court's position in *Markman II*, yet respects the traditional roles of trial and appellate courts. Thus

it is proposed that the standard of review of claim construction should vary with the source and purpose of the evidence, drawing analogy to review of the determination of obviousness under 35 U.S.C. §103. *See* Brief of Amicus Curiae American Bar Association at 12 ("it is well settled that Rule 52(a) governs appellate review of the factual inquiries underlying the ultimate legal issue of obviousness").

The third view

The third view, supported by some amici curiae, is that *Cybor* is both reasonable and correct in view of the Court's rulings in *Markman II*. These proponents stress the Court's statements that claim construction is a "purely legal" matter, 517 U.S. at 391, and that "the interpretation of a so-called patent claim is a matter of law," *id.* at 372. They argue that *de novo* review of the scope and meaning of patent claims conforms to the rule that applies in all areas of law, that "interpreting a set of legal words in order to determine their basic intent" is a "purely legal matter." *Buford v. United States*, 532 U.S. 59, 65 (2001). They state that sufficient reason has not been shown to change this established and effective precedent in patent cases.

In *Markman II* the Court placed claim construction in historical context, quoting Professor Robinson's treatise:

> The duty of interpreting letters-patent has been committed to the courts. A patent is a legal instrument, to be construed, like other legal instruments, according to its tenor .... Where technical terms are used, or where the qualities

> of substances or operations mentioned or any similar data necessary to the comprehension of the language of the patent are unknown to the judge, the testimony of witnesses may be received upon these subjects, and any other means of information be employed. *But in the actual interpretation of the patent the court proceeds upon its own responsibility, as an arbiter of the law, giving to the patent its true and final character and force.*

517 U.S. at 388 (quoting 2 W. Robinson, Law of Patents §732, pp. 481-83 (1890)) (emphasis the Court's). Proponents of retaining the *Cybor* standard point to the Court's emphasis that the judge is responsible for "the actual interpretation of the patent." *Id.* These proponents also point to the Court's citation to *Miller v. Fenton*, 474 U.S. 104 (1985) in support of the Court's ruling in *Markman II* that:

> [W]hen an issue "falls somewhere between a pristine legal standard and a simple historical fact, the fact/law distinction at times has turned on a determination that, as a matter of the sound administration of justice, one judicial actor is better positioned than another to decide the issue in question." So it turns out here, for judges, not juries, are the better suited to find the acquired meaning of patent terms.

Markman II, 517 U.S. at 388 (quoting *Miller*, 474 U.S. at 114). These proponents argue that *Miller* confirms that the Court in *Markman II* intended to decide—and effectively did decide—both the judge/jury question and the fact/law question, as well as the related question concerning appellate review.

The Court's reliance on *Miller* in *Markman II* illustrates the Court's recourse to general jurisprudence and practical considerations, suitably applied, in resolving patent issues. Proponents of adherence to *Cybor* point out that *Miller* reiterated the Court's recognition in *Pullman-Standard* that no principle will "'unerringly distinguish a factual finding from a legal conclusion.'" *Miller*, 474 U.S. at 113 (quoting *Pullman-Standard*, 456 U.S. at 288). Proponents apply that observation to criticize departure from *Cybor* that would add, to the already complex laws of claim construction, a new and uncertain and contentious inquiry into which aspects of a particular construction fall on which side of the fact-law line. These proponents state that *Cybor* is not subject to these difficulties, and that there is not sufficient reason to impose this new area of dispute and peripheral litigation upon the trial and appeal of patent cases.

The proponents of *stare decisis* point to the courts' and patent community's fifteen years of experience with *Cybor*, and argue that this experience supports retention of the *Cybor* principle. Emphasizing the potential multi-case and multi-forum litigation of patents on today's technologies, they argue that it is particularly important that this court be able to resolve claim construction definitively as a matter of precedent, rather than allow differing trial court constructions of the same patent, as may result from deferential review of close questions. As the Court observed in *Markman II*, "treating interpretive issues as purely legal will promote (though it will not guarantee) intrajurisdictional certainty through the application of *stare decisis* on those questions not yet

subject to interjurisdictional uniformity under the authority of the single appeals court." 517 U.S. at 391.

Thus it is argued that the meaning and scope of a patent claim, which sets the boundaries of an exclusionary right good against the world at large, rather than only for parties to a voluntary transaction or only for the plaintiff and defendant in a particular case, should be construed based on publicly available materials in the record, and resolved for uniform application throughout the nation, as a matter of law. No party or amicus disputed that the only way to achieve uniform construction of the same claim, a goal recognized in *Markman II*, is by *de novo* appellate construction of the claim as a matter of law. There is no dispute as to the importance of national uniformity and finality of claim construction, for it is not unusual for different district courts to litigate the same patent against different parties and different assertions of infringement.

In sum, these proponents argue that the *Cybor* standard of review of claim construction reasonably and appropriately implements the Court's ruling in *Markman II*, and urge this court to stand by *Cybor* and its fifteen years of experience. Proponents of stability through the principles of *stare decisis* stress that consistency of legal analysis and reliability of judicial process are foundations of not only legal systems generally, but also of the technological advance and industrial commitment that are goals of the patent system. *See* Brief of Amici Curiae Cisco et al. at 15 ("Competing and inconsistent interpretations of patent claims obscure the

boundaries of patents and deeply undermine their important notice function, inevitably resulting in more—rather than less—litigation."); *id.* at 19 ("Clear scope is important to all potential market entrants. This kind of horizontal certainty is important to the entire industry.").

The criticism of *Cybor* is not based on any demonstration that *de novo* claim construction is likely to be incorrect, but rather on concerns for judicial roles and relationships. We do not ignore these important concerns. However, as proponents of *stare decisis* point out, *Cybor* is narrowly focused on the threshold construction of a legal document, and does not affect the traditional deference to district court findings of infringement or validity or damages or any other question of fact in patent litigation. The proponents remind us that *Cybor* was adopted in implementation of the *Markman* decisions of this court and the Supreme Court, and is in accord with these rulings on the nature of the patent grant and the judicial obligation for correct determination of the legal scope of the patent grant.

Thus it is urged that the *Cybor* standard should not now be abandoned for a more costly and litigious standard, with diminished stability of procedure and diminished reliability of outcome, and no greater likelihood of correctness of result. These proponents point out that those who would change *Cybor*'s system of plenary review of claim construction have not shown any benefit or advantage to the law or those served by the law. Thus it is argued that the values of *stare decisis* counsel against overturning *Cybor*.

II

STARE DECISIS

The question now before this en banc court is not the same question that was before the en banc court in 1998 when *Cybor* was decided. The question now is not whether to adopt a *de novo* standard of review of claim construction, but whether to change that standard adopted fifteen years ago and applied in many hundreds of decisions. There has been extensive experience of *Cybor* in action, in the district court and on appeal. "Claim construction" has become the gateway issue in patent litigation, often decided in preliminary proceedings before trial and before discovery, and often subject to immediate appeal on summary judgment or injunction grounds. Such experience enriches the principle that courts will "stand by things decided" so that prior rulings may be relied upon.

Stare decisis is of "fundamental importance to the rule of law." *Hilton v. S. Carolina Pub. Ry. Comm'n*, 502 U.S. 197, 202 (1991) (quoting *Welch v. Texas Dep't of Highways & Pub. Transp.*, 483 U.S. 468, 494 (1987)). The doctrine of *stare decisis* enhances predictability and efficiency in dispute resolution and legal proceedings, by enabling and fostering reliance on prior rulings. *CSX Transp. Inc. v. McBride*, 131 S. Ct. 2630, 2641 (2011). By providing stability of law that has been decided, *stare decisis* is the foundation of a nation governed by law. The Supreme Court has said: "we will not depart from the doctrine of *stare decisis* without some compelling justification." Hilton, 502 U.S. at 202 (citing *Arizona v. Rumsey*, 467 U.S. 203, 212 (1984)); *see Dickerson v.*

United States, 530 U.S. 428, 443 (2000) ("special justification" is needed to overrule precedent).

Stability in procedural as well as substantive law, on which the public and the courts can rely, guards against the expenditure of time and resources on aspects that have been resolved. These values come to the fore when a court undertakes to reexamine its own precedent, for *stare decisis* implements the "prudential and pragmatic considerations designed to test the consistency of overruling a prior decision with the ideal of the rule of law, and to gauge the respective costs of reaffirming and overruling a prior case." *Planned Parenthood of S.E. Pa. v. Casey*, 505 U.S. 833, 854 (1992). The principles and policies of *stare decisis* operate with full force where, as here, the en banc court is considering overturning its own en banc precedent.

The presumption that a court will adhere to its prior rulings has "'special force'" for precedents that resolve non-constitutional issues, for "'Congress remains free to alter what we have done.'" *J.R. Sand & Gravel Co. v. United States*, 552 U.S. 130, 139 (2008) (quoting *Patterson v. McLean Credit Union*, 491 U.S. 164, 172-73 (1989)). In *Patterson* the Court observed that the same issue had previously divided the Court and that "[s]ome Members of this Court believe that [the precedent] was decided incorrectly"; the Court discussed the principles of *stare decisis*, and concluded that "no special justification has been shown for overruling" the prior decision, for neither "the growth of judicial doctrine or further action taken by Congress. have removed or weakened the conceptual underpinnings from the prior decision." 491 U.S. at 171-173. The Court observed

that no "later law has rendered the decision irreconcilable with competing legal doctrines or policies." *Id.* at 173.

In *Hohn v. United States*, 524 U.S. 236, 253 (1998) the Court discussed its precedent in light of *stare decisis*, and stated that "[o]nce we have decided to reconsider a particular rule, however, we would be remiss if we did not consider the consistency with which it has been applied in practice." In *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2067-68 (2011) the Court observed that although its prior decision on the same issue was "badly fractured," the majority holding "has become a fixture in the law," warranting application of the doctrine of *stare decisis*.

The purposes of consistency and stability that underlie *stare decisis* led to the formation of the Federal Circuit, now thirty years past, to provide consistency and stability to the patent law: "The central purpose is to reduce the widespread lack of uniformity and uncertainty of legal doctrine that exist in the administration of patent law," H.R. REP. 97-312, at 23 (1981), in view of the importance of technology-based advance to the nation's economy, *id.*; S. REP. 97-275, at 6 (1981) (same). Legal doctrine in patent law starts with the construction of patent claims, for the claims measure the legal rights provided by the patent.

In the Federal Circuit decision that led to the Supreme Court's *Markman II* ruling, this court explained that reviewing claim construction as a matter of law assures "a true and consistent scope of the claims." *Markman I*, 52 F.3d at 979. The Court

did not adjust or criticize that position, which forms the foundation of *Cybor*. *Cybor*, in carrying forward *Markman I* in light of *Markman II*, embodies the view that *de novo* review will "help institute a simplified and clarified method by which both trial and appellate courts address claim construction issues." *Cybor*, 138 F.3d at 1463 (Plager, J., concurring).

We do not ignore that neither *Cybor* nor the *Markman* decisions were free of contention, then as now. As we undertake this review of *Cybor*, we recognize that *stare decisis* is not an "inexorable command," *Agostini v. Felton*, 521 U.S. 203, 235 (1997). Thus we have considered whether there are sound reasons for this court now to depart from this precedent. We proceed with the guidance of history, experience, and the many amici curiae, while retaining awareness that to overturn an en banc ruling that has had long and wide application, there must be more than controversy about the prior rule. *See Watson v. United States*, 552 U.S. 74, 82 (2007) ("A difference of opinion within the Court does not keep the door open for another try."). As observed in *Morrow v. Balaski*, 719 F.3d 160, 181 (3d Cir. 2013) (Smith, J., concurring), "the very point of *stare decisis* is to forbid us from revisiting a debate every time there are reasonable arguments to be made on both sides."

However, departure from precedent may be appropriate when "subsequent cases have undermined [its] doctrinal underpinnings," *Dickerson*, 530 U.S. at 443; or when the precedent has proved "unworkable," *J.R. Sand & Gravel Co.*, 552 U.S. at 139; or when "a considerable body of new

experience" requires changing the law, *Pearson v. Callahan*, 555 U.S. 224, 234 (2009).

Stare decisis embraces procedural as well as substantive precedent. *Vasquez v. Hillery*, 474 U.S. 254, 266 (1986) (considering whether procedures have so far developed as to have left the old rule "outdated, ill-founded, unworkable, or otherwise legitimately vulnerable to serious reconsideration"); *Swift & Co. v. Wickham*, 382 U.S. 111, 116 (1965) (overruling procedural precedent where "unworkable in practice," among other problems). Procedures in the litigation-prone arena of patent rights can affect the cost, time, and uncertainty of litigation, and in turn affect economic activity founded on the presence or absence of enforceable patents. Courts should be "cautious before adopting changes that disrupt the settled expectations of the inventing community." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002).

Applying these premises, we have reviewed the arguments for changing the *Cybor* procedure of *de novo* review of claim construction. First, we have looked for post-*Cybor* developments, whether from the Supreme Court, from Congress, or from this court, that may have undermined the reasoning of *Cybor*. None has been found, or brought to our attention. There has been no legislative adjustment of the *Cybor* procedure, despite extensive patent-related legislative activity during the entire period of *Cybor*'s existence.

We have looked for some demonstration that *Cybor* has proved unworkable. No proponent of change has shown that *de novo* review of claim construction is

unworkable—nor could they, after fifteen years of experience of ready workability. Nor has anyone shown that *Cybor* has increased the burdens on the courts or litigants conducting claim construction.

To the contrary, reversing *Cybor* or modifying it to introduce a fact/law distinction has a high potential to diminish workability and increase burdens by adding a new and uncertain inquiry, not only on appeal but also in the trial tribunal. No consensus has emerged as to how to adjust *Cybor* to resolve its perceived flaws. Despite probing questioning at the en banc hearing, and despite the extensive amicus curiae participation, there is no agreement on a preferable new mechanism of appellate review of claim construction; there is no analysis of how deference would be applied to the diversity of old and new technologies and modes of claiming, no clear exposition of fact or law as could be applicable to the millions of unexpired patents, each on a different new technologic advance. As will be discussed, no one, including the dissent, proposes a workable replacement standard for *Cybor*, no workable delineation of what constitutes fact and what constitutes law.

Disentangling arguably factual aspects, some in dispute and some not, some the subject of expert or other testimony and some not, some elaborated by documentary evidence and some not, some construed by the district court and some not, some related to issues to be decided by a jury and some not—and further disentangling factual aspects from the application of law to fact—is a task ripe for lengthy peripheral litigation. We are not persuaded that we ought to overturn the en banc *Cybor* decision and

replace its clear *de novo* standard with an amorphous standard that places a new, cumbersome, and costly process at the gate, to engender threshold litigation over whether there was or was not a fact at issue. The principles of *stare decisis* counsel against such an unnecessary change.

No critic of *Cybor* has provided any analysis of specific claims or cases to show, or even to suggest, that deferential appellate review is more likely to achieve the correct claim construction. The principles of *stare decisis* counsel against overturning precedent when there is no evidence of unworkability and no clearly better resolution. The amici curiae agreed that modification of *Cybor* is unlikely to change many results, even if it could be defined well (which it has not been, by any amicus or by our colleagues in dissent).

Claim construction is a legal statement of the scope of the patent right; it does not turn on witness credibility, but on the content of the patent documents. The court may indeed benefit from explanation of the technology and the instruction of treatises, but the elaboration of experts or tutorial explanation of technical subject matter does not convert patent claim construction into a question of fact. The type of evidence that may assist a lay judge in determining what a technical term meant to one of skill in the art does not transform that meaning from a question of law into a question of fact. Reference to technical understanding and usage at the time of enactment does not convert statutory interpretation from law to fact. *See, e.g., Corning Glass Works v. Brennan*, 417 U.S. 188, 202 (1974) (applying "the

language of industrial relations" to statutory interpretation).

Courts routinely look to dictionaries and treatises to determine the meaning of a statute at the time it was written. *See, e.g., Sandifer v. U.S. Steel Corp.*, 134 S. Ct. 870 (2014) (looking to dictionaries to determine the meaning of "changing clothes" in the Fair Labor Standards Act at the time of enactment); *Comm'r v. Soliman*, 506 U.S. 168 (1993) (interpreting the tax code by looking to dictionary definitions at the time of enactment); *Chapman v. United States*, 500 U.S. 453 (1991) (using dictionaries to ascertain the ordinary meaning of "mixture" in the drug statute).

Similarly, experts in the science or technology may assist the court in understanding the meaning and usage of a claim term, but this does not morph the question into one of fact. *Cf. United States v. Stone & Downer Co.*, 274 U.S. 225 (1927) (relying on expert testimony on the meaning of the tariff term "clothing wool" in the custom of the trade). The Court stated in *Markman II*:

> in theory there could be a case in which a simple credibility judgment would suffice to choose between experts whose testimony was equally consistent with a patent's internal logic. But our own experience with document construction leaves us doubtful that trial courts will run into many cases like that. In the main, we expect, any credibility determinations will be subsumed within the necessarily sophisticated analysis of the whole document, required by the standard construction rule that a term can be defined only

> in a way that comports with the instrument as a whole.

517 U.S. at 389. This expectation has proven accurate. The presentation of expert testimony on the meaning of a claim term does not transform the question from one of law to one of fact.

We have carefully considered the arguments for discarding or modifying *Cybor*, and conclude that they do not justify departing from the now well-established principles and procedures. Under any standard of review consistent with *Markman II*, most issues of claim construction are indisputably matters of law, and would receive *de novo* review. Even the critics of *Cybor* agree that any change would affect only a small number of claim construction disputes. Statements at the en banc hearing are edifying; *e.g.*, Tr. at 1:14:10-1:14:35 (Appellant) ("This court could, in whatever it does with *Cybor*, make very clear that this battle of competing experts is rarely productive, rarely going to influence claim construction. If you said to me, why doesn't *stare decisis* carry the day? I don't have a good answer to that."); *id.* at 55:15-55:20 (United States) ("this court's law on claim construction requires very little modification"); *id.* at 1:06:50-1:07:30 (United States) (whether a term has special meaning in the art could be "meaningless ultimately" if inconsistent with the intrinsic record).

In response to a question at the hearing, amicus curiae United States could not identify any case that would have come out differently under the modified (hybrid) standard of review it proposed. Tr. at 1:07:30-1:08:00. Certainly *stare decisis* counsels

against overturning en banc precedent where doing so would change our known, workable *de novo* standard to an undefined alternative, sure to engender peripheral litigation, and which most agree could affect the outcome of very few, if any cases. *See Pearson*, 555 U.S. at 236-37 (criticizing precedent that "sometimes results in a substantial expenditure of scarce judicial resources on difficult questions that have no effect on the outcome of the case").

Claim construction is often a preliminary proceeding in the district court, before trial of infringement, validity, damages, etc. At the threshold, the court establishes the metes and bounds of the claims that define the patent right. The questions of claim construction are not questions of weight of evidence or credibility of witnesses, but of the claim scope as set forth in the patent documents.

Claim construction is the interpretation of a legal document that establishes a property right that applies throughout the nation. The question under review is whether this court, of nation-wide jurisdiction, should continue to review claim construction *de novo* with national effect, or whether to change to a system whereby a district court's claim construction is reviewed on the deferential standard appropriate to findings of fact, with or without some sort of hybrid deference to the ultimate determination. The insistence of some amici curiae that some form of deferential review is required as well as superior, is not only contrary to the *Markman* holdings, but to the experience of fifteen years of *Cybor*.

In the increasingly frequent situation where the same patent is litigated in different forums against different defendants, differing district court rulings on close questions of claim construction could well warrant affirmance on deferential review. Because differing claim constructions can lead to different results for infringement and validity, the possibility of disparate district court constructions unravels the "uniformity in the treatment of a given patent" that the Court sought to achieve in *Markman II*. 517 U.S. at 390. It would restore the forum shopping that the Federal Circuit was created to avoid. Just as the Court in *Markman II* counted such consequences as negatives that its ruling overcame, they count as negatives in the *stare decisis* analysis.

The question that this court has now reconsidered is whether we should continue to review claim construction as a whole and *de novo* on the record, or whether we should change to a different system that at best would require us to identify any factual aspects and how the trial judge decided them, and review any found or inferred facts not for correctness but on a deferential standard, with or without also giving deferential review to the ultimate determination of the meaning of the claims. We conclude that such changed procedure is not superior to the existing posture of plenary review of claim consturuction.

Over these fifteen years this court has applied *Cybor* to diverse subject matter, and the body of precedent has grown large. Deferential review does not promise either improved consistency or increased clarity. We have been offered no argument of public policy, or changed circumstances, or unworkability or

intolerability, or any other justification for changing the *Cybor* methodology and abandoning *de novo* review of claim construction.

The proponents of overruling *Cybor* have not met the demanding standards of the doctrine of *stare decisis*. They have not shown that *Cybor* is inconsistent with any law or precedent, or that greater deference will produce any greater public or private benefit. We conclude that there is neither "grave necessity" nor "special justification" for departing from *Cybor*.

III

REMARKS ON THE DISSENT

Our colleagues in dissent offer a few arguments that warrant response. First, referring to "the materials submitted to the court," the dissent states that "a substantial proportion of the legal community" believes that *Cybor* was "wrongly decided." Diss. at 6. The materials tell a different tale.

As listed *ante*, at n.2, thirty-eight organizations and individuals filed twenty-one amicus briefs. Contrary to the dissent's statements, all of the technology industries that offered advice to the court, urge retention of *Cybor*'s standard. These amici curiae include the largest technology companies in the nation, all involved with the system of patents, all frequent patent litigants both as plaintiffs and as defendants—unlike all of the other amici.[4] The

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[4] Amazon.com, Inc., Cisco Systems, Inc., Dell Inc., EMC Corporation, Google Inc., Hewlett-Packard Co., Intel

dissent dismisses these voices as merely "some amici" who support retention of *Cybor*, Diss. at 6, and offers no response to their concerns for stability, national uniformity, and predictability in claim construction.

The dissent appears unconcerned that the major industrial amici urge retention of the *Cybor* standard, and instead announces that "no one in the legal community— except perhaps the members of the majority—has come to believe that either the wisdom or vitality of *Cybor* is settled," Diss. at 6. This conclusion is curious. For example, the amicus brief of Google, Amazon, Hewlett-Packard, Red Hat and Yahoo! states that departing from *Cybor* would "make worse" the uncertainty of claim construction:

> [T]he root causes of uncertainty in claim construction are vaguely drafted claims and contradictory claim-construction methodologies, not appellate review. Deference would not ameliorate those causes of uncertainty; it would make them worse.
>
> * * *
>
> [T]reating claim construction as a factual question subject to clear-error review would only aggravate the uncertainty and cost issues plaguing our patent-litigation system.

Brief of Amicus Curiae Google et al. at 4, 5.

Corporation, Microsoft Corporation, SAP America Inc., Red Hat, Inc., and Yahoo! Inc. Other amici in support of preserving the full *Cybor* standard are the Austin Intellectual Property Lawyers Association and the Intellectual Property Institute at the William Mitchell College of Law.

The industrial amici also respond to the argument, pressed by the dissenters, that treating claim construction as a matter of law negates settlement and increases litigation cost. Diss. at 35. These litigants advise that the contrary is true:

> [C]lassifying claim construction as being at least partly factual would make patent litigation even more costly by discouraging courts from resolving claim construction disputes at the outset. Early claim construction is essential to permit the parties to file summary judgment motions, or to engage in informed settlement discussions, before they have to incur potentially unnecessary discovery and other pre-trial costs—costs that force many defendants to settle even meritless cases solely because the exorbitant cost of litigating a case would exceed the settlement amount demanded by the plaintiff.

Google et al. Br. at 4-5. Even Appellant's counsel at oral argument contradicted the cost-of-litigation and settlement arguments:

> A lot of commentators have said *Cybor* is preventing settlements: I don't believe that. I settle cases all the time. No one has ever focused primarily or even significantly on the standard of review on appeal. They're focused on the jury. They're focused on the cost of litigation. So a lot of what's been put up as reasons to change *Cybor* I don't think are there.

Tr. 1:14:40-1:15:05.

In the brief filed by Cisco, Dell, EMC, Intel, SAP, and the SAS Institute, these amici curiae suggest

that the proponents of overturning *Cybor* incorrectly conflate concepts of uncertainty with appellate reversal rates. These amici explain that any possible uncertainty of affirmance on appeal is not the issue in claim construction; rather, the issue is how to generate accuracy and uniformity in claim construction, that is, how to construe claims correctly and predictably.

> Clear scope is important to all potential market entrants. This kind of horizontal certainty is important to the entire industry. By contrast, the concern that *de novo* review increases the "duration" of a single patent litigation until a final decision is reached in that particular case (*Cybor*, 138 F.3d at 1476 (Rader, J., dissenting))—what might be called vertical uncertainty—matters only in the small fraction of cases that reach an appeal. Vertical uncertainty is more visible than horizontal uncertainty, but, as often is the case, here it is the unseen effects that are greater. *Cf. Frédéric Bastiat, What Is Seen and What Is Not Seen* (1848), available at http://www.econlib.org/library/-Bastiat/basEss1.html.
>
> For this reason, it is not merely the overarching principles of claim construction, but their application, that must be consistent. In claim construction as elsewhere, "the relevant legal principle can be given meaning only through its application to the particular circumstances of a case." *Miller*, 474 U.S. at 114.

Brief of Amicus Curiae Cisco et al. at 19.

The Cisco amici emphasize the Supreme Court's recognition of "the importance of uniformity" in *Markman II*, 517 U.S. at 390, and stress that treating claim construction issues as "purely legal," *id.* at 391, enables appellate review to supply that uniformity:

> Federal Circuit review, and in particular this Court's application of *stare decisis*, is critical to such uniformity. As the Supreme Court explained, "treating interpretive issues as purely legal" will allow *stare decisis* to be applied to those interpretive questions and thus promote uniformity among decisions of this Court (so-called "intra-jurisdictional certainty").

Cisco et al. Br. at 5 (citing and quoting *Markman II*, 517 U.S. at 391). These amici also discuss the "hybrid" proposal of some theorists, and state:

> "treating interpretive issues as purely legal" not as a mixed question—is the proper approach.

Id. at 5 (quoting *Markman II*, 517 U.S. at 391).

Amicus Microsoft discusses another aspect of the *Cybor* treatment of claim construction, advising that *de novo* review

> works well in practice because it allows the parties to address questions concerning claim scope in pre-trial hearings well in advance of the actual trial. Having a jury decide these re-designated factual matters could eliminate the current practice of pre-trial *Markman* hearings. This would exacerbate the expense and

> uncertainty in patent litigation and create new opportunities for forum shopping.

Brief of Amicus Curiae Microsoft at 3.

In sum, the amici curiae record of the nation's major innovators is contrary to the dissent's representation that "no one in the legal community—except perhaps the members of the majority—has come to believe that either the wisdom or vitality of *Cybor* is settled." Diss. at 6. The amici curiae record is contrary to the dissent's pronouncement that "the interests of stability and predictability are disserved" by *Cybor*'s access to final, uniform, national claim construction. Diss. at 29. The nation's major innovators do not agree with the criticisms of *Cybor*, and so advised the court. These amici direct the court to the pragmatic value of *Cybor* as they have experienced it, and urge retention of that value.

Rather than respond to the concerns of the nation's technology industries, the dissent chastizes certain judges of this court for not "acting on their long-term convictions." Diss. at 2. While it is comforting to know that our golden words of the past are not forgotten, those of us with the majority today who have questioned aspects of *Cybor* in the past, now decide this case on the record of the present and with an eye to the future. The dissent would discard the experience of the past fifteen years. However, the court is not now deciding whether to adopt a *de novo* standard in 1998. Today we decide whether to cast aside the standard that has been in place for fifteen years.

The dissent offers no superior alternative to *de novo* review, nor any workable standard for

distinguishing between legal and factual components of claim construction. The dissent does not appear to adopt the proposal of several amici that appellate deference should depend on whether the district court relied on intrinsic or extrinsic evidence in construing a claim term. It is surely doubtful that such a distinction controls whether claim construction is fact or law. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc) (discussing sources of evidence in claim construction, and stating "while extrinsic evidence 'can shed useful light on the relevant art,' we have explained that it is 'less significant than the intrinsic record in determining 'the legally operative meaning of claim language'") (citing cases). We have come upon no rationale for denominating an issue of claim construction as one of fact or law depending on the source of the information considered by the judge.

The dissent seems to embrace (then expand upon) the "historical fact" notion proposed by Appellant, who states that the meaning a person of ordinary skill in the art would give a term at the time of the filing of the patent application ought to be treated as a question of fact. This is not a question of fact; it is the very inquiry which determines the claim construction in nearly all cases. Claim terms are given their ordinary meaning to one of skill in the art, unless the patent documents show that the patentee departed from that meaning. *See Phillips*, 415 F.3d at 1314; *Thorner v. Sony Computer Entm't Am., LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). Treating the ordinary meaning to a skilled artisan as requiring deference would mean deference on the controlling question of claim construction in nearly

every case. All the more so with the dissent's proposed treatment of still additional issues, such as prosecution disclaimer, as warranting deference. Diss. at 42.

Under the dissent's approach, and even under the "historical fact" approach, deference would become of central significance in controlling the determination of claim construction, and hence of patent scope. The consequence would be heightened forum-shopping and the inability of the judicial system to arrive at a uniform, settled meaning for a patent's scope. Those problems are grave ones given the increasingly common situation of multiple cases involving the same patent.

The dissenters do not explain why they choose to abandon the benefits foreseen by the Court in *Markman II*, that "treating interpretive issues as purely legal" would have benefits of "intrajurisdictional certainty." 517 U.S. at 391. Nor have they successfully explained away the analysis in *Miller v. Fenton*, 474 U.S. at 113-14, that:

> [T]he practical truth that the decision to label an issue a "question of law," a "question of fact," or a "mixed question of law and fact" is sometimes as much a matter of allocation as it is of analysis . [T]he fact/law distinction at times has turned on a determination that, as a matter of the sound administration of justice, one judicial actor is better positioned than another to decide the issue in question.

(cited in *Markman II*, 517 U.S. at 388). The Court in *Miller* explained that the fact/law distinction is not immutable, and may invoke "the sound

administration of justice," *id.* at 114, leading to a similar acknowledgement in the *Markman II* ruling that claim construction is "a matter of law reserved entirely for the court." 517 U.S at 372.

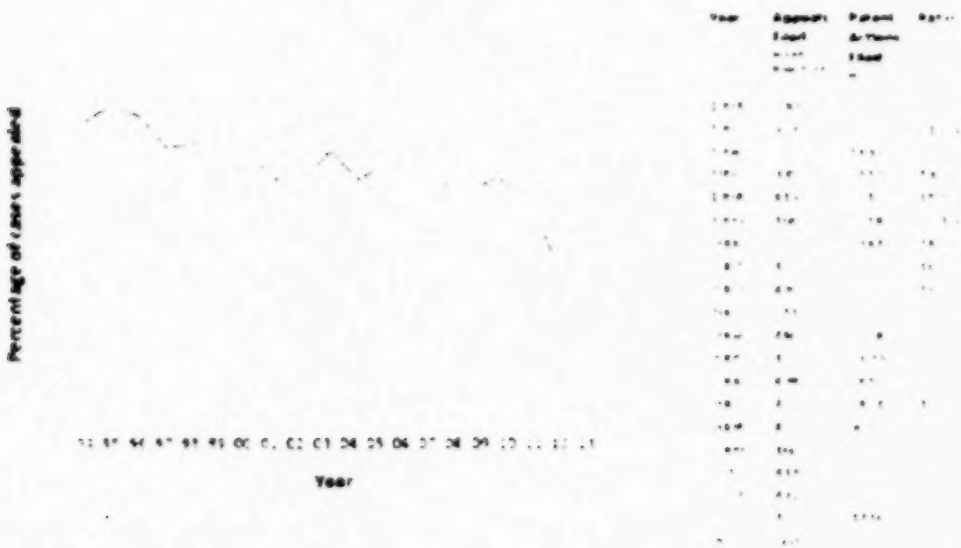
In addition, the dissent downplays the gravity of overturning a previous en banc court in the absence of intervening Supreme Court or legislative action. Of the several decisions of the Federal Circuit that the dissent cites as setting a pattern of overturning precedent, all involve en banc review of panel precedents, with the arguable exception of *Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059, 1068 & n.5 (Fed. Cir. 1998) (en banc in relevant part), where the court clarified that this court's law would govern the question of patent/antitrust immunity.

The major thrust of the dissent is that Federal Rule 52(a)(6) requires deferential review of district court decisions. But Rule 52(a) does not answer the question here. Rule 52(a) prescribes the standard of review of questions of fact, but courts must look outside the Rule to decide if a question is properly characterized as one of fact. As the Court stated in *Pullman-Standard*, 456 U.S. at 288, "Rule 52(a) does not furnish particular guidance with respect to distinguishing law from fact. Nor do we yet know of any other rule or principle that will unerringly distinguish a factual finding from a legal conclusion." The dissent's theory that Rule 52(a) demands abandonment of *de novo* review of claim construction is a simplistic disregard of the *Markman II* guidance that "treating interpretive issues as purely legal will promote (though it will not guarantee) intrajurisdictional certainty." 517 U.S. at 391.

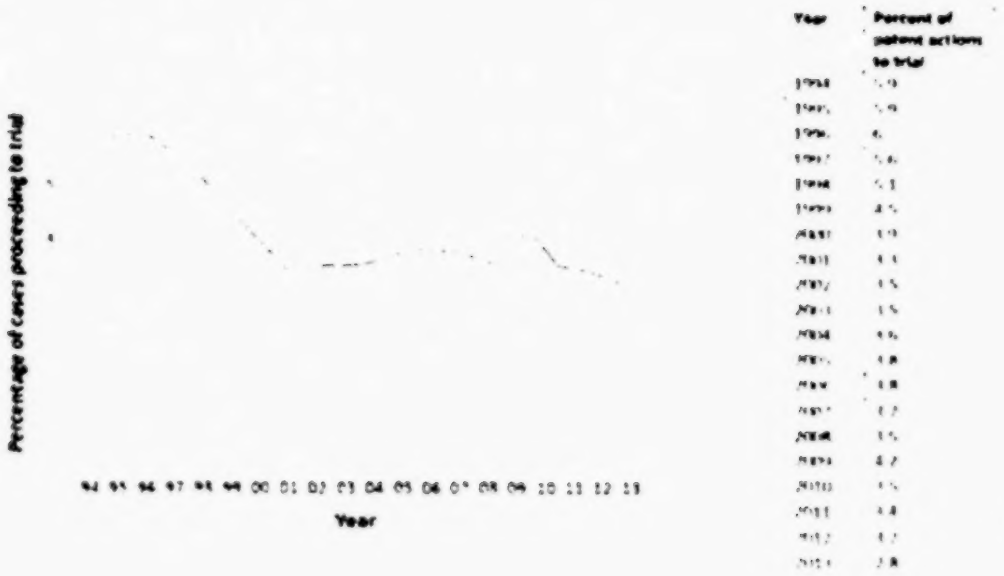
The dissent argues that *de novo* review produces a high reversal rate, although it is established that this is no longer true. The reversal rate indeed was a matter of concern, for in the early years of *Cybor*, this court's promulgation of claim construction law led to a higher rate of appellate adjustment. However, as consistency evolved and experience grew, rates of appellate reversal for claim construction came to match the norm for other grounds. We observe that every amicus brief that complains about high reversal rates relies on data that are seven to ten or more years old, while the author of a recent study writes in his amicus brief that the data "document a significant drop in the claim construction reversal rate" since 2005, Brief of Amicus Curiae Professor Peter Menell at 15, and explains in his study that "[n]ow the reversal rate for claim construction appeals is much closer to that of other patent-related issues." J. Jonas Anderson & Peter S. Menell, *Informal Deference: An Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 Nw. U. L. Rev. (forthcoming), Sept. 9, 2013 manuscript at 37.

Our colleagues in dissent, citing the obsolete data, argue that the *de novo* standard "adds considerable uncertainty and expense to patent litigation," Diss. at 4, stating that this standard increases appeals, discourages settlement, and increases the length and cost of litigation. No evidence of this effect is offered, and all of the amici curiae who are frequent litigants state the contrary position. The data published by the Administrative Office of the United States Courts point the other way. These data show a long, noticeable decline in the percentage of district court

patent cases that are appealed, belying the argument that appeals have increased. The following data are from the Annual Reports of the Administrative Office for the years 1994 to 2013. The graph shows the ratio, as a percentage, of the number of patent appeals filed per year (Report Table B-8), against the number of district court patent cases filed in that year (Report Table C-2):



The Annual Reports also show the trend in the percentage of patent cases that proceed to trial in the district courts. The data from Table C-4 in the Reports show the percentage declining from 5.9% in 1994 to 2.8% in 2013:



The data do not support the dissent's theory that *Cybor* has increased patent litigation and inhibited settlements. In contrast, the industrial amici curiae advise the court that the *Cybor* review procedure assists in resolving litigation before full trial or extensive discovery, for it often leads to the grant of summary judgment and an immediate appeal. These amici stress that settlement is facilitated by final resolution of the scope of the claims. They also point out that if the claim construction is definitively resolved, any ensuing trial is on the final claim construction. The dissent does not comment on these values.

CONCLUSION

We have again considered the standard of review of district court claim construction rulings, in light of experience with the *Cybor* standard. The ever-enlarging importance of technology-based industry in the economy has reinforced the need for an optimum patent system.

On thorough review, we are not persuaded that discarding *de novo* review would produce a better or more reliable or more accurate or more just determination of patent claim scope. Those who urge change in the *Cybor* standard have identified no pattern of error, no indictment of inferior results. No ground has been shown for departing from the principles of *stare decisis*. Review of claim construction as a matter of law has demonstrated its feasibility, experience has enlarged its values, and no clearly better alternative has been proposed. There has arisen no intervening precedent, no contrary legislation, no shift in public policy, no unworkability of the standard.

We conclude that the criteria are not met for overruling or modifying the *Cybor* standard of *de novo* review of claim construction as a matter of law.

PANEL DECISION REINSTATED

No costs.

LOURIE, *Circuit Judge*, concurring.

I fully agree with the majority opinion and join it. I write separately to note what I believe are additional reasons why retaining *Cybor* is wise.

First and foremost is that the Supreme Court has held that claim construction is a question for the court rather than the jury. Thus, for us to appear to be cutting back from that holding by giving formal deference on so-called fact-like questions, which normally would go to the jury, to the district court judge, would seem to me to be an attempt to partially retreat from the Court's holding, which is unwise.

We have held that claim construction is a question of law, going only minimally beyond the Court's explicit holding that it is only a question for the court. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454-55 (Fed. Cir. 1998) (en banc). The Court's holding, including its statement that it is a "mongrel" question, does not encourage fractionation of the process, making part of it subject to *de novo* review and part clearly erroneous review. The Court in *Markman* stated that construction of terms of art should be ceded to the judge "notwithstanding its evidentiary underpinnings." The "notwithstanding" applies to any factual as well as legal aspects of claim construction. Evidentiary underpinnings do not lean toward a clearly erroneous standard any more than they do to the jury.

Equally important, one of the purposes of Congress in creating our court was to achieve uniformity in the patent law. Consistent with that goal should be uniformity of interpretation in construction of patent claims. It is not rare that a patent is asserted against more than one defendant in different forums, with conflicting holdings on infringement. It would hardly promote uniformity of patent law for us to bless a claim construction in one district court, based on that court's judging the credibility and demeanor of the expert witnesses in one case, when a different case might lead to a different result based on a different district judge's appraisal of different witnesses. We in fact might be confirming conflicting claim constructions, the antithesis of uniformity. This problem might increasingly exist in light of the AIA's limits on the number of accused infringers that can be joined as defendants in one

lawsuit, thereby creating the possibility of more lawsuits on the same patent, and more inconsistency, than existed in the past. *See* 35 U.S.C. § 299(a); *In re EMC Corp.*, 677 F.3d 1351 (Fed. Cir. 2012).

By our deferring to those determinations, conceding our full review of the meaning of a claim term, which should be based on the patent's written description and prosecution history, not the witnesses, hampers our ability to interpret claims with full authority and hence to ensure uniformity.

Furthermore, claim construction is not a process that normally involves historical facts. It primarily involves reading the patent's written description as well as the prosecution history of the patent, and this court is quite as able to do that as any district court, sometimes better. It is true that there may be questions concerning what a particular claim term meant to one skilled in the art at a particular time, but, in my view, when the trial judge is subjected to dueling experts selected for their views, choosing which of them to credit hardly amounts to historical fact-finding. To the extent that it does, the relevant inquiry should be, not what the dueling experts say, but what the inventor understood the term to mean when he or she filed the patent application containing the claim term in question. Courts should be reluctant to go beyond the written record to help answer that question. It is too subject to ex post facto thinking based on self-interest; the inventor had his chance to define his invention and should not be heard in later testimony to get another bite at the apple by redefining that language.

A realistic assessment of the problem in claim construction in litigation recognizes that the patenting process begins with an inventor and his or her attorney drafting a written description and claims to describe and specifically claim his or her invention. The claims will usually then get negotiated in the Patent Office. The issued claims are then used, pursuant to some perceived business need or desire, by a different lawyer who had no part in the drafting of the written description and claims, who then tries in front of a lay judge to shoehorn an accused infringer into claims that usually do not fit (or else claim construction and infringement would not be at issue).

Hired "experts," supporting the parties' theories of infringement or non-infringement take positions that are also distinct and isolated from (and often different from) those originally taken by the inventor and attorney, who knew what the invention was and what positions were taken in the Patent Office during prosecution. Thus, the problem lies, not with lack of deference to district court interpretation of claims by the Federal Circuit, but to the multiplicity of actors contending in a competitive economy. The actors striving to deal with a patent in district court are often not those who made the invention, created the patent, and hence knew exactly what it meant. The solution does not lie in depriving the one institution charged with ensuring uniformity of part of its authority.

Much criticism has been directed at this court for allegedly ignoring all the fine work of district court judges in construing patent claims. That criticism is premised on the misperception that we do not give a

district court's claim construction any deference. That is incorrect; perhaps one even might say "clearly erroneous."

The rubric governing issues of law unfortunately does read "no deference." But even though we all know that the rubric governing procedural errors is the harsh "abuse of discretion" language, all judges know that a finding of a procedural error does not normally justify the term "abuse." Similarly, the "no deference" language is simply established legal jargon for a holding that, having reviewed the record, we disagree. It has been stated in some amicus briefs before the court that there are truly factual issues involved in claim construction, particularly what a claim term meant to one skilled in the art at a particular time, and that such a determination should be given deference. But we should not complicate the law and change our precedent for such a situation. This court should rarely overturn a district court's claim construction on a finding of that nature.

This appellate court, when asked to interpret the claims of a patent carefully, notes and considers how the district court construed the claims. If we disagree, it is not without a degree of informal deference. Claims are to be interpreted in light of the written description in the patent specification, and in light of the prosecution. The choice of expert witnesses by parties' counsel, and their demeanor, do not override those basic documents. Very few scientists called as expert witnesses will lie, hence the term "credibility," useful in more conventional fact determinations, such as whether a traffic light

was red or not, should not be controlling in construing claim limitations in a patent.

Claim construction is analogous to interpretation of other legal instruments, such as contracts and legislation. Each of these determinations is for the court, not a jury, although each can be found to contain factual components (it should be noted though that, at least in patent prosecution, the intent of neither the inventor-attorney nor the patent examiner is usually at issue in claim construction). Thus, beyond what the Court has held in *Markman*, there is good analogical basis for considering claim construction as similar to interpretation of these other legal instruments. Moreover, to the extent that underlying considerations create the "mongrel" nature of claim construction, considering factual components to be subject to deference under a clearly erroneous rule would implicate the Seventh Amendment right to a jury trial on factual questions. Such a procedure would further threaten the uniformity that Congress intended in setting up this court as well as the Supreme Court's ruling that claim construction is not for the jury.

What the proponents of splitting construction into legal and factual issues are in essence contending for is that some issues in patent infringement are for the judge (some claim construction issues), some are also for the judge, but are of a factual nature, ordinarily as for a jury, and some clearly for the jury, *i.e.*, infringement. However, in claim construction, simpler is better—claim construction in all its aspects for the judge, subject to review by the appellate court, with sensible reliance on the prior work of the trial judge. Creating a formal distinction

between fact-sounding issues subordinate to claim construction and the ultimate claim construction is a complication that we should not foist on this court.

A further point is that ultimately it should not matter whether claim construction has a factual component to which formal deference attaches or not. If, as I believe we should, and do, give proper informal deference to the work of judges of a subordinate tribunal, then we will or should affirm when affirmance is appropriate. If, on the other hand, we were to apply a more formal clearly erroneous standard, judgments of subordinate courts are still not unreviewable. If we were to find that the so-called factual component, based on our review of the intrinsic record, has been determined incorrectly, clearly we could find it to be incorrect even with a clearly erroneous standard. Thus, this is an argument that should not much matter.

Moreover, to the extent we were to overrule *Cybor*, or modify it, and give formal deference to district courts, but reserve the right to decide the ultimate issues of obviousness and validity as questions of law, we would be engaging in a kind of sham, giving with one hand and taking back with the other. Doing so would bow to what amounts to a cosmetic public, or judicial, exercise in order to overcome the harsh rubric of "no deference."

To the extent that critics assert that *de novo* review has not achieved the goal of uniformity, I believe that deferring to district court judges on subsidiary, extrinsic fact-related issues, and relying on experts hired for having positions favorable to particular parties would likely result in even less

uniformity. At least under our current regime, claim construction in all its aspects is reviewed by one appellate court. And providing formal deference to district courts in evaluating fact-related issues would encourage migration away from reliance on the intrinsic written record of the patent specification and its prosecution history.

One should also make no mistake about it: if deference were to be given to rulings on complicated subject matter, intensive appellate review would fade away (how many appeals from the PTO are now reversed following *Zurko's* increase in the degree of deference given to the relatively expert examining agency?), and so will uniformity. In addition, if determining whether an issue is fact or law would determine the degree of deference granted, parties would be arguing over that question, as in appeals in veterans cases, rather than the real merits of claim construction. As for the relatively high reversal rate of claim construction at this court, I very much doubt that it is primarily due to so-called issues of historical fact; they are primarily due to our court's review of the claims in light of the specification, not to failure to judge the credibility of contending expert witnesses. Besides, the reversal rate on claim construction is apparently coming down. *See* J. Jonas Anderson & Peter S. Menell, *Informal Deference: An Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 Nw. U. L. Rev. _, 1 (forthcoming 2014).

This case did not involve subsidiary findings resolving disputes of historical fact. What was involved was whether there was corresponding structure to support "voltage source means" for

"providing a constant or variable magnitude DC voltage between the DC input terminals" The panel found the means clause in the claim lacked sufficient structure, and the specification similarly was lacking, so it reversed the district court on the ground that the claims were indefinite. Historical fact-finding was not involved; reading the claims and written description was. The en banc court should arrive at the same conclusion, as the district court did not rely on any subsidiary findings of fact. How a means plus function term is construed under § 112, ¶ 6 is not fact, but claim construction, *i.e.*, law.

For the above reasons, in addition to the majority's reliance on the doctrine of *stare decisis*, I support the court's decision not to overrule *Cybor*.

O'MALLEY, *Circuit Judge*, dissenting, with whom RADER, *Chief Judge*, REYNA and WALLACH, *Circuit Judges*, join.

District judges, both parties in this case, and the majority of intellectual property lawyers and academics around the country will no doubt be surprised by today's majority opinion—and for good reason. The majority opinion is surprising because it refuses to acknowledge what experience has shown us and what even a cursory reading of the Supreme Court's decision in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), confirms: construing the claims of a patent at times requires district courts to resolve questions of fact. And, it puts itself at odds with binding congressional and Supreme Court authority when it refuses to abide by the requirements of Rule 52(a)(6) of the Federal Rules of Civil Procedure, which expressly instructs

that, on appeal, *all* "findings of fact must not be set aside unless clearly erroneous." It is also surprising because, having, for the third time, invited a broad swath of the intellectual property community to express opinions regarding the merits of *Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc), we now premise our refusal to change its holding on principles of stare decisis—that, and a professed inability to come up with a workable alternative to de novo review.[1]

Criticism of and debate over *Cybor* have been widespread since it issued—not only among legal scholars and patent practitioners, but also among members of this court. Despite this fact, the majority suggests, for the first time in the ongoing debate over it, that *Cybor* is too firmly established in our case law to be rethought. In fact, it appears that some members of today's 6-4 majority believe the pull of *stare decisis* is so strong that it prevents them from acting on their long-term convictions that *Cybor* was wrongly decided. No reasoned application of stare decisis principles supports that conclusion.

To the extent the majority is motivated not just by a resistance to change, but by concern over what standard we should change to, those concerns can be allayed by reference to Rule 52(a)(6) of the Federal Rules of Civil Procedure, the Supreme Court's case law governing that rule, and a realistic assessment of what the claim construction process entails.

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[1] We invited and received input regarding the standard of review to be applied to claim construction in *Cybor* itself, in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), and now in this case.

Because principles of stare decisis do not justify retention of the rule of *Cybor* and the appropriate standard of review is dictated by Rule 52(a), I respectfully dissent.

I.

In *Cybor*, this court held that claim construction, "including any allegedly fact-based questions relating to claim construction," presents "a purely legal question" subject to de novo review. *Cybor*, 138 F.3d at 1456. We reached that conclusion even though, in *Markman*, the Supreme Court repeatedly acknowledged the factual component of claim construction. There, the Court: (1) labeled claim construction as a "mongrel practice," (2 suggested that construing a patent's claims "falls somewhere between a pristine legal standard and a simple historical fact," (3) indicated that "there could be a case in which a simple credibility judgment would suffice to choose between experts whose testimony was equally consistent with a patent's internal logic," (4) discussed the need "to ascertain whether an expert's proposed definition fully comports with the specification and claims," and (5) described claim construction's "evidentiary underpinnings." *Markman*, 517 U.S. at 378, 388-90 (citation and internal quotation marks omitted). Despite being urged to do so by *both* parties, the Patent and Trademark Office, and multiple amici, the majority refuses to overturn *Cybor*.[2] The majority rests its

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[2] The majority describes three views espoused by the parties and amici, giving substantially more attention to the one that is consistent with the result the majority reaches. Careful review of the materials submitted to the court, and of the many

judgment primarily on the principles of stare decisis. It asserts that our fifteen years of experience with *Cybor* teach that our continued de novo review of all claim construction determinations is needed to assure greater "reliability of outcome" and "interjurisdictional uniformity." Maj. Op. at 14, 16.

Considerations of stare decisis, however, do not justify adhering to precedent that misapprehends the Supreme Court's guidance, contravenes the Federal Rules of Civil Procedure, and adds considerable uncertainty and expense to patent litigation.

II.

Stare decisis is an important part of our jurisprudence, and departing from our precedent is not something we should do lightly. The doctrine "promotes the even-handed, predictable, and consistent development of legal principles, fosters reliance on judicial decisions, and contributes to the actual and perceived integrity of the judicial process." *Payne v. Tennessee*, 501 U.S. 808, 827 (1991). It also serves to guard against "arbitrary discretion." *Hubbard v. United States*, 514 U.S. 695, 711 (1995) (citations and internal quotation marks omitted).

"Stare decisis is not an inexorable command[, however]; rather it 'is a principle of policy and not a mechanical formula of adherence to the latest

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academic and legal writings regarding *Cybor* since its issuance, show that a substantial portion of the legal community to have considered the issue believes *Cybor* was wrongly decided and flies in the face of Rule 52 of the Federal Rules of Civil Procedure.

decision.'" *Payne*, 501 U.S. at 828 (quoting *Helvering v. Hallock*, 309 U.S. 106, 119 (1940)). Its force varies from case to case, moreover— carrying the most weight where reliance interests are at stake, but the least weight where the departure from precedent would not change substantive rights and would "not affect the way in which parties order their affairs." *Pearson v. Callahan*, 555 U.S. 223, 233 (2009); *see also Payne*, 501 U.S. at 828. "Revisiting precedent is particularly appropriate where a departure would not upset expectations and experience has pointed up the precedent's shortcomings." *Pearson*, 555 U.S. at 233. The Supreme Court has noted that departing from precedent especially is appropriate "when governing decisions are badly reasoned." *Payne*, 501 U.S. at 827 ("[W]hen governing decisions are unworkable or are badly reasoned, 'this Court has never felt constrained to follow precedent.'" (quoting *Smith v. Allwright*, 321 U.S. 649, 665 (1944))); *see also Helvering*, 309 U.S. at 119 (cautioning against blindly applying stare decisis when adhering to precedent would "involve[] collision with a prior doctrine more embracing in its scope, intrinsically sounder, and verified by experience").

Consistent with this Supreme Court guidance, we have explained that stare decisis does not stand in the way of abrogating our case law—even entire bodies of it— in at least three circumstances: when we conclude our case law (1) was wrongly decided, *see, e.g.*, *Wilson v. United States*, 917 F.2d 529, 536 (Fed. Cir. 1990) (en banc); (2) is at odds with congressional directives, *see, e.g.*, *Akamai Technologies, Inc. v. Limelight Networks, Inc.*, 692 F.3d 1301, 1318 (Fed. Cir. 2012) (en banc); or (3) has

had negative consequences, *see, e.g.*, *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1288 (Fed. Cir. 2011) (en banc). With these principles in mind, this court has not hesitated to revisit its own precedent. *See, e.g.*, *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 576 F.3d 1348 (Fed. Cir. 2009) (en banc); *In re Seagate Tech., LLC*, 497 F.3d 1360 (Fed. Cir. 2007) (en banc); *Fisher v. United States*, 402 F.3d 1167 (Fed. Cir. 2005) (en banc); *Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp.*, 383 F.3d 1337 (Fed. Cir. 2004) (en banc). Indeed, we have said that it is "'[t]he province and obligation of the en banc court to review the current validity of challenged prior decisions.'" *Robert Bosch, LLC v. Pylon Mfg. Corp.*, 719 F.3d 1305, 1316 (Fed. Cir. 2013) (en banc) (quoting *United States v. Aguon*, 851 F.2d 1158, 1167 n.5 (9th Cir. 1988) (en banc)). And, we have made clear that this includes overturning precedent set by this court en banc when appropriate. *See Nobelpharma USA, Inc. v. Implant Innovations, Inc.*, 141 F.3d 1059, 1068 (Fed. Cir. 1998) (overruling *Atari, Inc. v. JS & A Grp., Inc.*, 747 F.2d 1422 (Fed. Cir. 1984) (en banc), by "chang[ing] our precedent and hold[ing] that whether conduct in procuring or enforcing a patent is sufficient to strip a patentee of its immunity from the antitrust laws is to be decided as a question of Federal Circuit law").

Thus, both Supreme Court case law and our own teach that it is in cases like this one that stare decisis is weakest.

III.

Reversing *Cybor* will not "upset settled expectations on anyone's part." *Pearson*, 555 U.S. at 233. The one thing clear about *Cybor* is that no one in the legal community—except perhaps the members of the majority— has come to believe that either the wisdom or vitality of *Cybor* is settled. Whether one urges the retention of the holding in *Cybor* (as do some amici) or urges its revision (as do the parties, the Patent and Trademark Office, and the rest of the amici), it is hard to dispute that tumult has surrounded *Cybor* since it was decided. During its short life, *Cybor* repeatedly has been criticized as poorly reasoned. That criticism has come from members of this court, from district court judges, and from academics and practitioners across the country.

Our internal debate over *Cybor* has been heated, and has not abated over time. There were several ardent detractors from the rule announced in *Cybor* at the time it was announced. *See, e.g.*, *Cybor*, 138 F.3d at 1478, 1480 (Newman, J., additional views) ("By continuing the fiction that there are no facts to be found in claim interpretations, we confound rather than ease the litigation process. However, the Supreme Court has relieved us of adherence to this fiction, by its recognition of the factual component of claim interpretation."), *id.* at 1463 (Mayer, C.J., concurring in the judgment) (stating that the *Cybor* majority opinion "profoundly misapprehends" the Supreme Court's decision in *Markman*); *id.* at 1473 (Rader, J., dissenting from the pronouncements on claim interpretation in the en banc opinion, concurring in the judgment, and joining part IV of the en banc opinion). Even some of

the less vocal critics who concurred in the result in *Cybor* expressed hesitation regarding the wisdom of either the rule established or the legitimacy of its underpinnings. *See id.* at 1463 (Plager, J., concurring) ("Whether this approach to patent litigation will in the long run prove beneficial remains to be seen."); *see also id.* at 1463 (Bryson, J., concurring) ("[W]e approach the legal issue of claim construction recognizing that with respect to certain aspects of the task, the district court may be better situated than we are, and that as to those aspects we should be cautious about substituting our judgment for that of the district court.").

Since *Cybor*, our internal debate has continued. In *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), the order granting rehearing en banc asked the parties to address whether it is "appropriate for this court to afford any deference to any aspects of trial court claim construction rulings." *Id.* at 1328. Despite receiving considerable input from the parties and amici, the *Phillips* majority, without explanation, "decided not to address that issue at this time." *Id.* In dissent, however, Judge Mayer levied a pointed criticism of *Cybor*, (1) discussing "the absurdity[] of this court's persistence in adhering to the falsehood that claim construction is a matter of law devoid of any factual component," (2) stating that, "[i]n our quest to elevate our importance, we have disregarded our role as an appellate court undermin[ing] the legitimacy of the process, if not the integrity of the institution," and (3) observing that "we are obligated by Rule 52(a) to review the factual findings of the district court that underlie the determination of claim

construction for clear error." *Id.* at 1330, 1332 (Mayer, J., dissenting).

We have revisited the question multiple times since then: (1) in 2006 in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039 (Fed. Cir. 2006); (2) in 2011 in *Retractable Technologies, Inc. v. Becton, Dickinson & Co.*, 659 F.3d 1369 (Fed. Cir. 2011); and (3) even as recently as a year ago in *Highmark, Inc. v. Allcare Health Management Systems, Inc.*, 701 F.3d 1351 (Fed. Cir. 2012), where questions of claim construction were not even at issue. *See, e.g., Amgen*, 469 F.3d at 1043 (Newman, J., dissenting from denial of reh'g en banc) ("The Federal Circuit's position that patent interpretation requires more rigorous appellate review than other fact/law issues has not withstood the test of experience. It is time to reopen the question and to rethink, *en banc*, the optimum approach to accuracy, consistency, and predictability in the resolution of patent disputes "); *id.* at 1046 n.3 (Moore, J., dissenting from denial of reh'g en banc) (highlighting the problems *Cybor* has caused for district courts attempting to construe patent claims); *id.* at 1045 (Gajarsa, Linn, & Dyk, JJ., concurring in denial of reh'g en banc) (noting that the concurrence "should not be read as an unqualified endorsement of the en banc decision in *Cybor*"); *Retractable Techs.*, 659 F.3d at 1373 (Moore, J., dissenting from denial of reh'g en banc) ("The Supreme Court held that claim construction was a 'mongrel practice.' As such it is clearly a mixed question of law and fact and deference should be given to the factual parts. [W]e must acknowledge the factual underpinnings of this analysis and there should be deference."

(citation omitted)); *Highmark*, 701 F.3d at 1362 (Moore, J., dissenting from denial of reh'g en banc) (citing to *Cybor* and stressing that "[w]e need to avoid the temptation to label everything legal and usurp the province of the fact finder with our manufactured *de novo* review").

Notably, not once during this internal dialogue over the rule promulgated in *Cybor* did anyone contend that stare decisis alone should put an end to our debate. Two members of the current majority have been among the harshest critics of *Cybor*—contending on multiple, and even recent, occasions that it was poorly reasoned, impractical, and should be reversed. A third conceded that *Cybor*'s rule may be too broad and perhaps should not apply where, as here, the trial court was forced to resort to extrinsic evidence to assess the meaning of claim terms. In none of their discussions of *Cybor* was concern regarding stare decisis raised. It certainly was never exalted to the hard stop on further consideration of Cy-bor's merits that the majority now finds it to be.

And, the debate over *Cybor* has not all been internal to our court. The external debate has been both consistent and widespread. *See, e.g.*, Amicus Br. of United States, *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, No. 11-1154, 2012 WL 5940288, at *20-21 (U.S. Nov. 28, 2012) (setting out the Solicitor General's observation that (1) "*some* claim-construction decisions will depend on a district court's resolution of factual questions," (2) this court's "decision in *Cybor* does not identify any reason that such factual findings should not be given the deference ordinarily required by Federal Rule of Civil procedure 52(a)," and (3) "appellate courts

routinely defer to factual findings made by district courts and juries"). District judges have opposed de novo review, describing it as ill-conceived and illogical. *See, e.g., Amgen, Inc. v Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 226 n.23 (D. Mass. 2004)) (describing the "conundrum" our claim construction jurisprudence has created by "discouraging resort to extrinsic evidence while at the same time urging courts to begin claim construction by considering the plain and customary meaning of a term *as understood by one skilled in the art*"); Judge James F Holderman & Halley Guren, *The Patent Litigation Predicament in the United States*, Univ. Ill. J.L., Tech. & Pol'y 1, 6-7, 14-15 (2007) (noting that "claim construction involves many of what one would consider to be factual determinations," stressing that the Supreme Court in *Markman* "said nothing about the de novo standard of review," and calling for a more deferential review of district court claim constructions); *The Honorable William G. Young & Professor R. Carl Moy, Panel Discussion, High Technology Law in the Twenty-First Century: Second Annual High Technology Law Conference*, 21 Suffolk Transnat'l L. Rev. 13, 19 (1997) (statements of the Honorable William G. Young).

As have practitioners. *See, e.g.*, Frederick L. Whitmer, *Claim Construction in Patent Cases: A Question of Law?*, 2 No. 6 Landslide 14, 16-17 (2010) (criticizing our court's interpretation of the Supreme Court's guidance in *Markman* and calling for recognition of "the constituent factual component of claim construction decision making"); Donald R. Dunner & Howard A. Kwon, *Cybor Corp v. FAS*

Technologies: The Final Say on Appellate Review of Claim Construction?, 80 J. Pat. & Trademark Off. Soc'y 481, 492 (1998) ("[Notwithstanding its decision that claim construction was an issue for the judge and not the jury, the Court in *Markman II* seemed to consider the issue a mixed question of law and fact—a characterization that would resist straightforward application of the de novo standard."); Luke L. Dauchot, *The Federal Circuit's De Novo Review of Patent Claim Construction: A Need for a More Balanced Approach*, 18 Am. Bar Ass'n Sec. Pub. I.P.L. 1, 4 (1999) ("A proper approach recognizes that patent claim interpretation is 'a mongrel practice' and delegates the fact-finding process to trial courts ").

Academics have been particularly harsh in their criticism of *Cybor* and have suggested that we reverse it. *See, e.g.*, J. Jonas Anderson & Peter S. Menell, *Informal Deference: An Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 Nw. U. L. Rev. (forthcoming), Sept. 9, 2013 manuscript at *57-59 (arguing that *Cybor* "misapprehends" Supreme Court precedent, "deprive[s] the district court of critical evidence bearing on claim meaning," and "undermines the appellate process" by leaving "[t]he parties, the public, and the appellate court" with an "anemic record—typically limited to the intrinsic evidence"); Eileen M. Herlihy, *Appellate Review of Patent Claim Construction: Should the Federal Circuit Be Its Own Lexicographer in Matters Related to the Seventh Amendment?*, 15 Mich. Telecomm. Tech. L. Rev. 469, 515 (2009) ("A de novo standard of review runs contrary to the repeated and consistent word choices

made by the Court indicating that the Court considers claim construction to be a mixed issue of fact and law."); Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, 9 Lewis & Clark L. Rev. 231, 231 (2005) (observing the "concern among the bench and bar that the Federal Circuit's de novo review of district court claim construction decisions ha[s] caused considerable unpredictability"); John R. Lane & Christine A. Pepe, *Living Before, Through, and With Markman: Claim Construction as a Matter of Law*, 1 Buff. Intell. Prop. L.J. 59, 71 (2001) ("In *Markman II*, the Supreme Court did concede that there are factual underpinnings to claim construction determinations, raising the logical question of whether de novo review is the appropriate standard." (footnote omitted)).

In short, the only expectation about *Cybor* that appears "settled" is the expectation that one day this court might recognize that *Cybor* is inconsistent with Supreme Court precedent, the Federal Rules of Civil Procedure, and the practical realities involved in the claim construction process, and would reverse it.

Parties do not make claim drafting decisions based on the standard of review we apply to trial court claim constructions. Nor could they given the panel-dependent nature of our own determinations. *See* Donald R. Dunner, *A Retrospective of the Federal Circuit's First 25 Years*, 17 Fed. Cir. B.J. 127, 130 (2007) (noting that many believe "that Federal Circuit predictability is not what it should be and that its decisions are often panel-dependent and result-oriented"); R. Polk Wagner & Lee Petherbridge, *Is the Federal Circuit Succeeding? An*

Empirical Assessment of Judicial Performance, 152 U. Pa. L. Rev. 1105, 1112 (2004) ("Our findings indicate that claim construction at the Federal Circuit is panel dependent."). It is difficult to accept the proposition that our claim construction jurisprudence is a measure against which litigants make important business or innovation decisions. Claim construction disputes are very fact specific—patents do not follow a formulaic structure, or even contain oft repeated language. Claims are drafted, redrafted, and amended in ways intended to reflect and capture particular inventions in a particular field, to avoid very specific prior art, and to respond to the rejections of the unique patent examiner involved in the application process. It is rare that any two claims we review contain the same phrasing, and even more rare that the context in which the phrasing is used would not alter the meaning of even almost identical words.[3] *Compare Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342-43 (Fed. Cir. 2008) (finding that, as a general rule, the words "an" or "a" in a patent claim carry the meaning of "one or more"), *with TiVo, Inc. v. EchoStar Commc'ns Corp.*, 516 F.3d 1290, 1303 (Fed. Cir. 2008) (finding that "whether 'a' or 'an' is treated as singular or plural depends heavily on the context of its use" and concluding that "claims and written

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[3] There are, of course, some common patent terms that have been given universal meanings, or been characterized as open-ended, rather than exclusive. These are terms like "comprising," "consisting of," and "consisting essentially of." The meanings of most of these transitional terms were common to the patent drafting art well before this Circuit was formed. And, litigants and district courts are well aware of these conventions.

description in this case make clear that the singular meaning applies"). Combining the uniqueness of each claim term to be reviewed with the variations in rationale employed by the divergent members of this court, provides little practical guidance regarding how any claim construction dispute might be resolved in this forum—and certainly not the uniform reliability of outcome with which the majority now credits our jurisprudence in this area.

The fact that we have been engaging in a flawed practice for too long does not, alone, create the type of settled expectations stare decisis is meant to protect. Because settled expectations will not be disrupted and no substantive rights will be reordered, stare decisis simply does not stand in the way of this court addressing the merits of *Cybor* and acknowledging that the rule of law pronounced therein is an incorrect one.

IV

It is also clear that stare decisis does not stand in the way of overturning *Cybor* because *Cybor* is predicated on a mischaracterization of the Supreme Court's guidance in *Markman* and ignores the claim construction process we have ordered district courts to employ. In short, it need not be followed because its premises are wrong. *See Wilson*, 917 F.2d at 536 (overruling precedent that misconstrued congressional intent).

As noted above, *Cybor* misapprehends the Supreme Court's decision in *Markman*, ignoring numerous instances where the Court acknowledged that claim construction can present factual questions. The

Supreme Court did not base its conclusion on the fact that a patent is a legal instrument whose construction presents a *pure* question of law. If it had, there would have been no need for the Court to conduct such a thorough analysis of whether the Seventh Amendment required a jury to resolve issues of claim construction. That question would have needed no discussion if claim construction were purely an issue of law because juries have never been tasked with resolving purely legal questions. *See Markman*, 517 U.S. at 37684; *see also Cybor*, 138 F.3d at 1464 (Mayer, C.J., concurring in the judgment) ("Though it could have done so easily, the Court chose not to accept our formulation of claim construction: as a pure question of law to be decided *de novo* in all cases on appeal. If it had, there would have been no need for its extensive exegesis about the Seventh Amendment and whether juries must construe claims that have evidentiary underpinnings or whether the importance of uniformity is best served by giving these evidentiary questions of meaning to a judge." (footnote omitted)).

While *Cybor* dismissed *Markman*'s discussion of the factual aspects of claim construction as mere "prefatory comments," 138 F.3d at 1455, and insisted that, under *Markman*, claim construction is a completely legal exercise subject to de novo review, *id.* at 1456, that conclusion does not flow from *Markman*. There, the Supreme Court not only acknowledged claim construction's factual aspects, it also said nothing to suggest that a de novo standard of review would be appropriate. *See Retractable Techs.*, 659 F.3d at 1373 (Moore, J., dissenting from denial of reh'g en banc) ("The Supreme Court held

that claim construction was a 'mongrel practice.' As such it is clearly a mixed question of law and fact and deference should be given to the factual parts." (citation omitted)). *Markman*'s holding was limited to the Court's determination "that the construction of a patent, including terms of art within its claims, is exclusively within the province of the court." *Markman*, 517 U.S. at 372. There are many circumstances in which trial judges act as triers of both fact and law; in all of those, deference to the factual components of that decision-making is undoubtedly due. "Stating that something is better decided by the judge is not the same as saying it is a matter of law." *Highmark*, 701 F.3d at 1362 (Moore, J., dissenting from denial of reh'g en banc).[4] And even saying something is a matter of law does not answer the question of the standard of review an

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[4] This mistake is one repeated in some of the amicus briefs that support retention of *Cybor*, stating that *Cybor* must be retained so as to avoid having to submit claim construction issues to the jury. *See* Amicus Br. of Microsoft Corp. at 4-5; Amicus Br. of Intellectual Prop. Inst. of William Mitchell Coll. of Law at 10-12. But, the Supreme Court made clear in *Markman* that it had institutional efficiency reasons for taking claim construction away from the jury, unhampered as it was by Seventh Amendment concerns; the decision to give claim construction to trial judges did not turn on a fact/law distinction. *See Markman*, 517 U.S. at 384 n.10 ("Because we conclude that our precedent supports classifying the question as one for the court, we need not decide either the extent to which the Seventh Amendment can be said to have crystallized a law/fact distinction . or whether post-1791 precedent classifying an issue as one of fact would trigger the protections of the Seventh Amendment if (unlike this case) there were no more specific reason for decision." (citations omitted)). Because the views of these amici are based on this legally flawed premise, undue reliance on them is misplaced.

appellate court should apply. *See Pierce v. Underwood*, 487 U.S. 552, 560, 562 (1988) (observing that, "[i]n some cases, such as the present one, the attorney's fee determination will involve a judgment ultimately based on a purely legal issue governing the litigation," but concluding that "sound judicial administration counsels[] deferential review of a district court's decision regarding attorney's fees" despite its legal character).

Those amici who find great significance in the Supreme Court's citation to *Miller v. Fenton*, 474 U.S. 104 (1985), in *Markman* miss the mark. That citation does not, as those amici claim, decide the fact/law question or the question of the appropriate level of appellate review of claim construction determinations. In *Miller*, the Supreme Court concluded that the ultimate question of whether a confession was sufficiently voluntary to comport with due process, while a mixed question of fact and law, was subject to independent federal review. As the Court noted in *Markman*, it had concluded in *Miller* that, where a question "falls somewhere between a pristine legal standard and a simple historical fact," the conclusion as to which judicial actor is best positioned to decide a question at times turns on the sound administration of justice, rather than a pure fact/law distinction. 517 U.S. at 388. Though, in *Miller*, the Court decided that the sound administration of justice supported the conclusion that the ultimate constitutional question of whether a confession was voluntary should be reserved for federal, rather than state, courts, *Miller* says nothing about the standard of review one federal tribunal should apply to the inquiries of another, or how the

sound administration of justice would divvy up the responsibility of claim construction as between the trial and appellate courts.

In fact, in *Miller* itself, the Court concluded that a presumption of correctness still must be afforded to all "subsidiary factual questions" decided by the state courts. 474 U.S. at 112. And, the Court was careful to explain that its determination of what the sound administration of justice called for vis-à-vis the federal and state courts was reached in the absence of congressional directives to the contrary.

In *Markman*, the Supreme Court said that judicial efficiencies supported allocation of claim construction determinations to the court rather than the jury. It did not say that "subsidiary factual determinations" made by trial courts ceased to be subject to the deference congressionally mandated by the Federal Rules of Civil Procedure, however. And, it did not say that it was *this court* and *only this court* to which the question should be allocated. Indeed, in *Cooter & Gell v. Hartmarx Corp.*, 496 U.S. 384 (1990), decided five years after *Markman*, the Court addressed the question of how the sound administration of justice can impact the standard of review of questions that involve both factual and legal components. There, while the Court acknowledged that some purely legal inquiries are involved in determinations pursuant to Rule 11 of the Federal Rules of Civil Procedure, it found that the entire determination must be reviewed by the courts of appeals under an abuse of discretion standard. *Id.* at 403-04. Returning to the same type of inquiry employed in *Miller*, the Supreme Court explained that where, as in a Rule 11 inquiry, the line between fact and law is difficult to

divine and the trier of fact needs flexibility to decide unique facts that resist generalization, it is the trial judge who is the judicial actor best suited to decide the question. *Id.* In such instances, the Court found that the sound administration of justice to which it harkened in *Miller* and again in *Markman* mandated a fully deferential standard of review.

It is notable that at least one Supreme Court Justice on the Court when *Markman* was decided believes that, if *Markman* can be said to have decided the standard of review to be applied to claim construction determinations, it decided that question very differently than we did in *Cybor* and than we continue to do today. In *Gasperini v. Center for Humanities, Inc.*, 518 U.S. 415 (1996), dissenting from the judgment there, Justice Stevens described the Court's decision in *Markman* as one of three that term in which courts of appeals were "assigned the task of independently reviewing similarly mixed questions of law and fact," and described the nature of that review as one in which appellate courts are required "to construe all record inferences in favor of the factfinder's decision and then to determine whether, on the facts found below, the legal standard has been met." *Id.* at 442-43 (Stevens, J., dissenting).

Markman's citation to *Miller*, accordingly, lends no support to the notion that *Markman* somehow dictated the result in *Cybor*. It only helped explain why the court, rather than the jury, was chosen as the appropriate decision maker. *Cybor* was not compelled by the Supreme Court's guidance; as explained in section V below, it is actually a wide departure from it.

Cybor also ignores the realities of the claim construction process. As our en banc court in *Phillips* observed:

> [B]ecause extrinsic evidence can help educate the court regarding the field of the invention and can help the court determine what a person of ordinary skill in the art would understand claim terms to mean, it is permissible for the district court in its sound discretion to admit and use such evidence. In *exercising that discretion*, and *in weighing all the evidence bearing on claim construction*, the court should keep in mind the flaws inherent in each type of evidence and *assess that evidence accordingly*.

415 F.3d at 1319 (emphases added). *Cybor* cannot be squared with this court's own well-respected description of the very claim construction process to which it purports to apply.

The majority concedes that claims are to be interpreted from the perspective of one of skill in the art at the time of the invention unless it appears from the surrounding record—the specification and prosecution history— that the patentee acted as his own lexicographer to provide a contrary meaning. Maj. Op. at 32 (citing *Phillips*, 415 F.3d at 1314). It concludes, however, that all we need to put ourselves into the shoes of a skilled artisan are the patent documents and, perhaps (though not necessarily), some explanation regarding the technology at issue and a dictionary or treatise. It believes we do not need to hear from experts regarding the state of the known science or art at the time of the invention, the commonly understood meaning, if any, of the

particular terms or phrases employed, the level of education and skill one reading such a patent would have, or whether there are particular treatises or dictionaries to which a skilled artisan would have turned at the time. *See id.* at 22. And, it believes that the conclusions it gleans from the patent documents, including the entirety of the prosecution history, expert descriptions of the technology, and dictionaries are all legal conclusions; that no finding made by any judicial officer in the process of claim construction constitutes a subsidiary factual one. *See id.* at 22-23.

The majority justifies these conclusions by analogizing the claim construction process to the interpretation of statutes, where courts routinely consider contemporaneous dictionaries or even the testimony of historians to help determine the meaning of words and phrases therein. *See id.* The analogy is not a sound one, however.

Statutes are duly enacted laws of broad applicability. Their interpretation by an appellate court is binding on all who would be impacted by that statute in that circuit, whether parties to the original action or not. They are drafted by those with congressional authority to enact such laws and are to be given a meaning common to all. Patents are drafted *ex parte*, are revised in a closed-door examination process, their terms are, as noted before, unique to the invention at issue, and are assertable only against individual infringers in private actions. The two are simply not of the same ilk. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 998 n.8 (Fed. Cir. 1995) (Mayer, J., concurring in the judgment) ("Patents cannot be

baby statutes. "); *Amgen*, 469 F.3d at 1040-41 (Michel, C.J., dissenting from denial of reh'g en banc) (observing that, in statutory interpretation, a judge construes terms from the perspective of a skilled legal artisan looking at the words only, not from the perspective of a different individual—one skilled in the relevant field of technology in light of the intrinsic and extrinsic record).

The parties agree that there were disputed factual questions in this case that required examination of extrinsic evidence. In the proceedings before the district court and again on appeal, the parties disputed whether the claim term "voltage source means" should be treated as a means-plus-function limitation under 35 U.S.C. § 112, ¶ 6. *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 498 F. App'x 986, 989-90 (Fed. Cir. 2013). The use of the word "means" triggers the presumption that the limitation is a means-plus-function term, but that presumption "may be rebutted if the claim itself recites sufficient structure for performing the function." *Id.* at 990. The parties focused on whether "voltage source means" denoted a particular structure to those of skill in the art (i.e., whether the term had a specific meaning used by those of skill in the art to describe a defined structure or specific class of structures). *See id.* If skilled artisans understood "voltage source means" to refer to a defined structure, it would not be considered a means-plus-function limitation. *Id.* The specification and prosecution history, however, did not resolve the question. Thus, it became necessary and appropriate to look outside the intrinsic record and to consider the testimony of Lighting Ballast's expert, Dr.

Roberts. *See id.*; *see also Rembrandt Data Techs., LP v. AOL, LLC*, 641 F.3d 1331, 1341 (Fed. Cir. 2011) ("When determining whether a claim term recites sufficient structure, we examine whether it has an understood meaning in the art."). When situations like this arise, it is appropriate—and sometimes necessary—to make findings based on extrinsic evidence that relate to the meaning of a disputed term. Resolution of these fact-intensive disputes is an area where district courts' expertise deserves the deference that Rule 52(a)(6) requires.

Both parties, the PTO, and most amici agree that there are factual components to claim construction. Even among the amici that favor retaining *Cybor*'s de novo review of all aspects of claim construction, most readily identified factual questions that arise during claim construction. Microsoft Corp., for instance, advocated retaining *Cybor*, but nonetheless listed numerous factual questions that it concedes could arise during claim construction and would require the court to:

> determin[e] the field[s] of the invention and the knowledge of a person having ordinary skill in the art; determin[e] the art-accepted meanings of terms used in an issued claim and also used in the specification and/or prior art; determin[e] the date of the invention and/or the effective filing date of the patent application; determin[e] whether a proposed construction would exclude all embodiments in the specification or, conversely, whether any embodiment supports the construed issued claim; identifying explicit or implicit definitions in the specification; [and] determin[e] the disclosure of cited prior art

> references (which are part of the 'intrinsic evidence' for claim construction) asserted as invalidating prior art and/or distinguished in the prosecution history.

Amicus Br. at 4-5. Similarly, the Austin Intellectual Property Law Association observed that "district courts are charged with taking evidence of specialized meanings in patent interpretation." Amicus Br. at 8. Likewise, the brief filed by Cisco Systems, Inc. et al. acknowledged that a case could arise where "a question of meaning peculiar to a trade or profession [could] turn[] on the resolution of contested questions of historical fact."

Amicus Br. at 24-26 (citation and internal quotation marks omitted).

In sum, it is hard to understand how either the majority in *Cybor* or the majority here can dispute that claim construction sometimes requires a district court to resolve contested factual issues. *Cybor* is, thus, based on a faulty premise—that claim construction is a purely legal exercise. This reveals deep flaws in *Cybor*'s reasoning, justifying a departure from it. *See Payne*, 501 U.S. at 827 (permitting departure from decisions that prove "unworkable or are badly reasoned").

V.

Stare decisis also must give way because, by refusing to acknowledge the factual component of claim construction, *Cybor* contravenes the clear directives of Federal Rule of Civil Procedure 52(a)(6). When a district court makes findings of fact—as claim construction sometimes requires—Rule

52(a)(6) provides clear instructions to this court: "Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous " The rule is clear on its face, and decisions interpreting it show that it makes no exception with regard to fact-finding in the claim construction context. As the Supreme Court has observed, "Rule 52(a) broadly requires that findings of fact not be set aside unless clearly erroneous. It does not make exceptions or purport to exclude certain categories of factual findings from the obligation of a court of appeals to accept a district court's findings unless clearly erroneous." *Pullman-Standard v. Swint*, 456 U.S. 273, 287 (1982); *see also Bose Corp. v. Consumers Union of U.S., Inc.*, 466 U.S. 485, 498 (1984) ("We have repeatedly held that Rule [52(a)] means what it says."). Thus, there is direct conflict between *Cybor*—which expressly calls for de novo review of "any allegedly fact-based questions relating to claim construction," 138 F.3d at 1456—and Rule 52(a)(6)—which requires deference to *all* fact-findings that are not clearly erroneous. *See* Amicus Br. of United States at 9-13 (noting that "[a]ppellate courts must defer to a trial court's factual findings under Rule 52(a)" and that, "[g]iven the clear command of Rule 52(a), no justification exists to treat claim construction any differently").

The law governing obviousness confirms Rule 52(a)'s broad applicability in patent disputes. Obviousness presents a question of law subject to de novo review, but it involves a number of subsidiary fact-findings. As the Supreme Court observed:

> While the ultimate question of patent validity is one of law, the § 103 condition lends itself to several basic factual inquiries. Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent are resolved.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17 (1966). According to the Court, "[t]his description of the obviousness inquiry makes it clear that whether or not the ultimate question of obviousness is a question of fact subject to Rule 52(a), the subsidiary determinations of the District Court, at the least, ought to be subject to the Rule." *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 811 (1986); *see also Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987) ("Rule 52(a) is applicable to all findings on the four inquiries listed in *Graham*: scope and content of prior art; differences between prior art and claimed invention; level of skill; and objective evidence "). Importantly, one of the key fact questions in an obviousness inquiry is what a prior art reference teaches—often, what is claimed and described in a previously issued patent. *See Graham*, 383 U.S. at 17. And, all findings regarding the scope and content of the prior art are subject to clear error review. *See Panduit*, 810 F.2d at 1569. That we trust jurors to define the scope of patent claims in this context, but are less than comfortable allowing trial judges to do the same when considering the asserted patent claims is at least anomalous. *Cybor* is thus out of step with our other jurisprudence that faithfully applies Rule 52(a) in patent cases.

This conflict between *Cybor* and the Federal Rules of Civil Procedure means our case law must fall. As this court has observed,

> The Federal Rules of Civil Procedure were promulgated by the Supreme Court pursuant to statutory authority and were implicitly adopted by Congress after transmission to Congress in their proposed form. *See* 28 U.S.C. §§ 2071-2074. In light of this statutory promulgation scheme, the Supreme Court has held that the Federal Rules of Civil Procedure are deemed to have "the force [and effect] of a federal statute."

Bright v. United States, 603 F.3d 1273, 1279 (Fed. Cir. 2010) (alteration in original) (quoting *Sibbach v. Wilson & Co.*, 312 U.S. 1, 13 (1941)). Our cases dealing with the application of stare decisis where statutory interpretation is at issue thus provide useful guidance.

We often have held that stare decisis does not prevent our court from overturning its precedent when we conclude our prior jurisprudence runs contrary to what we believe are a statute's directives. *See, e.g., Akamai Techs., Inc. v. Limelight Networks, Inc.*, 692 F.3d 1301, 1306 (Fed. Cir. 2012) (en banc) (overruling multiple decisions of this court where "we held that in order for a party to be liable for induced infringement, some other single entity must be liable for direct infringement"); *Wilson v. United States*, 917 F.2d 529, 536 (Fed. Cir. 1990) (en banc) (overturning our earlier decision in *Ulmet v. United States*, 822 F.2d 1079 (Fed. Cir. 1987), saying: "We have revisited the legislative history of [10 U.S.C.] § 1163(d) in this case. Our examination has brought to

light that the legislative history of the sanctuary provision demands a different result from that reached in *Ulmet*."); *Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 576 F.3d 1348 (Fed. Cir. 2009) (en banc) (overruling prior case law because we believed that case law did not properly interpret 35 U.S.C. § 271(f)). In all of these instances, we concluded that stare decisis did not provide a basis for adhering to precedent that ran counter to the dictates of a statute, as properly interpreted.

We should bring our case law in line with the directives of Rule 52(a)(6), as we are required to do, and as we have done with respect to numerous statutory commands in the past. *See* Amicus Br. of United States at 9-13 (urging the court to overturn *Cybor* because it runs counter to Rule 52(a)'s clear commands); Amicus Br. of Am. Bar Ass'n at 12-13 (same); Amicus Br. of Prof. Peter Menell at 17-20 (In light of Rule 52(a)'s commands, "the Federal Circuit must defer to trial judges' factual determinations in claim construction rulings."); Amicus Br. of Am. Intellectual Prop. Law Ass'n at 4-6, 6 n.6 ("There is no reason for the review of patent claim construction, where the trial court makes constituent determinations of fact, to be any different from review of other ultimate issues of law that have factual underpinnings."); Amicus Br. of Fed. Cir. Bar Ass'n at 7; Amicus Br. of Intellectual Prop. Owners Ass'n at 7 (stressing that Rule 52(a) requires deference to district courts' findings of claim construction facts); Amicus Br. of Conn. Intellectual Prop. Law Ass'n at 12 (faulting *Cybor* for "say[ing] that patent cases have their very own Fed. R. Civ. P. 52(a)(6)," even though there is "no legitimate reason

to treat patent cases differently from other cases"); Amicus Br. of Fed'n Internationale Des Conseils en Propriete Intellectuelle at 12 (noting that de novo review of findings of claim construction facts "violates Federal Rule of Civil Procedure 52(a)(6)").

The majority discounts concerns about the dictates of Rule 52(a)(6) by citing the Supreme Court's statement in *Pullman-Standard v. Swint* that Rule 52(a) does not provide a clear formula for distinguishing fact from law. Maj. Op. at 34 (citing *Pullman-Standard*, 456 U.S. at 288). As the Court made clear in *Pullman-Standard* itself when reversing the Fifth Circuit's refusal to give deference to a trial court's factual inquiry, the fact that our inquiry might be a difficult one does not excuse the failure to undertake it. *See Pullman-Standard*, 456 U.S. at 288-90. Indeed, the Supreme Court has on numerous occasions charged the courts of appeals with drawing distinctions between subsidiary or "historical facts" and the ultimate legal conclusion regarding the import of those facts, and with adjusting their standard of review accordingly. *See Cooper Indus., Inc. v. Leatherman Tool Grp., Inc.*, 532 U.S. 424, 440 n.14 (2001) ("While we have determined that the Court of Appeals must review the District Court's application of the *Gore* test [set out in *BMW of North America, Inc. v. Gore*, 517 U.S. 559 (1996),] *de novo*, it of course remains true that the Court of Appeals should defer to the District Court's findings of fact unless they are clearly erroneous."); *Ornelas v. United States*, 517 U.S. 690, 699 (1996) (holding that "determinations of reasonable suspicion and probable cause should be reviewed *de novo* on appeal" but "hasten[ing] to point

out that a reviewing court should take care both to review findings of historical fact only for clear error and to give due weight to inferences drawn from those facts by resident judges and local law enforcement officers"); *Thompson v. Keohane*, 516 U.S. 99, 110-12 (1995) (concluding that there are two distinct inquiries—one purely factual and another a mixed question—involved in "[t]he ultimate 'in custody' determination for *Miranda* purposes," with deference to findings on all factual components due). As the PTO explains, "Congress gave no indication in the patent laws that it intended to displace the fundamental principle of appellate review for clear error." Amicus Br. of United States at 12.[5]

VI.

The "undesired consequences" flowing from this court's claim construction jurisprudence also justify departing from the law set out in *Cybor*. *Cybor*, 138

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[5] The scope of this court's obligation to abide by the dictates of Rule 52(a)(6) is currently before the Supreme Court. In *Highmark Inc. v. Allcare Health Management Systems, Inc.*, 687 F.3d 1300 (Fed. Cir. 2012), *cert. granted*, 134 S. Ct. 48 (Oct. 1, 2013) (No. 12-1163), the question presented is "[w]hether a district court's exceptional-case finding under 35 U.S.C. § 285, based on its judgment that a suit is objectively baseless, is entitled to deference." Petition for Writ of Certiorari, *Highmark Inc. v. Allcare Health Mgmt. Sys., Inc.*, 2013 WL 1209137, at *i (U.S. Mar. 25, 2013) (No. 12-1163). The petitioner asserts that deference must be given to all aspects of a district court's § 285 determinations because, among other reasons, there are subsidiary findings of fact which Rule 52(a)(6) demands be reviewed for clear error. *See id.* at *19-20. If the Supreme Court premises its holding in *Highmark* entirely or even partially on the dictates of Rule 52(a)(6), such a ruling would make clinging to *Cybor* for no reason other than a resistance to change completely untenable.

F.3d at 1481 (Newman, J., additional views); *see also Pearson*, 555 U.S. at 233 (stating that revisiting case law is "particularly appropriate" where experience has revealed its shortcomings). By refusing to acknowledge the factual component of claim construction, *Cybor* has made the claim construction process less transparent, accurate, predictable, and efficient, thereby imposing high "social costs." *See* Anderson & Menell, *supra*, at *60-61; Whitmer, *supra*, at 16 (lamenting the "high reversal rate" with respect to claim construction that is the "consequence of the *Cybor* uncertainty principle"); Lane & Pepe, *supra*, at 71-73 (examining the uncertainty that results from de novo review).

A.

The primary interests furthered by stare decisis—a doctrine rooted in policy—support departing from *Cybor*, not adhering to it. *See Helvering*, 309 U.S. at 119 (observing that stare decisis "is a principle of policy"). Preserving the stability of the law and protecting the public's ability to "rel[y] on judicial decisions" are the central interests furthered by stare decisis. *Payne*, 501 U.S. at 827. By withholding deference to district courts' findings of claim construction facts, however, the interests of stability and predictability are disserved. *See Highmark*, 701 F.3d at 1362 (Moore, J., dissenting from denial of reh'g en banc) ("When we convert factual issues, or mixed questions of law and fact, into legal ones for our *de novo* review, we undermine the uniformity and predictability goals this court was designed to advance."); *see also* Amicus Br. of Prof. Peter Menell at 15 (observing that "[t]he[] effects [of de novo review of claim construction determinations]

continue to cast doubt on the predictability of patent litigation, discourage settlements following claim construction trial, delay resolution of patent disputes, and run up the overall costs of patent litigation"). Indeed, our resistance to changing *Cybor* is directly contrary to the purposes of Rule 52(a)(6): to promote stability in the judicial system by (1) avoiding undermining the legitimacy of district courts and (2) preventing unnecessary appeals by discouraging appellate retrial of factual issues. *See* Fed. R. Civ. P. 52 advisory committee's note (1985).

Under the *Cybor* regime, a district court can construe a claim term, and an entire trial can follow premised on that construction. When the district court's judgment is appealed, however, we review every aspect of its claim construction de novo, leaving us largely free to reinterpret claims—both upsetting parties' expectations and undoing a tremendous amount of parties' and district courts' work in the process. *See Cybor*, 138 F.3d at 1476 (Rader, J., dissenting from the pronouncements on claim interpretation in the en banc opinion) ("To get a certain claim interpretation, parties must go past the district court's *Markman I* proceeding, past the entirety of discovery, past the entire trial on the merits, past post-trial motions, past briefing and argument to the Federal Circuit— indeed past every step in the entire course of federal litigation, except Supreme Court review."). Once here, moreover, as noted earlier, "[c]ommentators have observed that claim construction appeals are 'panel dependent' which leads to frustrating and unpredictable results for both the litigants and the trial court." *Retractable Techs.*, 659 F.3d at 1370 (Moore, J., dissenting from

denial of reh'g en banc) (citations omitted). And, while the majority says that it is "no longer true" that there is a high reversal rate with respect to claim constructions by district courts, Majority Opinion at 34, that is not what trial judges, litigants, and academics contend. As Professor Peter Menell says in his amicus brief before this court: "Although we document a significant drop in the claim construction reversal rate since the *Phillips* decision, there still remains a high reversal rate compared to other areas of federal practice." [6] Amicus Br. at 15; *see also* Amicus Br. of Ass'n of Bar of N.Y. ("The high reversal rate of the district court claim construction, documented in numerous studies, is universally acknowledged. It is not an overstatement to conclude that the reversal rate has had a detrimental effect on the parties, the court, and the credibility of the patent system generally." (footnote omitted)). Departing from *Cybor* and reviewing claim construction findings for clear error would introduce *greater stability* and less expense, and would afford the appropriate respect for district courts' factual determinations—respect that Rule 52(a)(6) demands. As a consequence, this case presents an instance where overturning this court's

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[6] The majority is incorrect that "every amicus brief that complains about high reversal rates relies on data that are seven to ten or more years old." Maj. Op. at 34. Professor Menell's amicus brief to this court describes his recent research with Professor Jonas Anderson, which reveals that de novo review of claim construction continues to contribute to "alarming levels of appellate reversals." Amicus Br. at 13-14; *see also* Anderson & Menell, *supra*, at *6 (examining this court's claim construction jurisprudence from 2000 through 2011).

precedent will lead to *greater* stability and predictability, not *less*.

B.

Refusing to acknowledge that claim construction has a factual component effectively "deprives th[is] court, and the parties, of the accumulated progress and experience of the trial, including the findings of the trial judge, and leaves us on appeal with an expurgated record and generally inferior basis of decision." *Cybor*, 138 F.3d at 1481 (Newman, J., additional views). By affording zero deference to any aspect of a district court's claim construction, we ignore the reality that we lack the tools that district courts have available to resolve factual disputes fairly and accurately. As Judge Rader observed in dissenting in part in *Cybor*,

> the trial judge enjoys a potentially superior position to engage in claim interpretation. For the complex case where the claim language and specification do not summarily dispose of claim construction issues, the trial court has tools to acquire and evaluate evidence that this court lacks. Trial judges can spend hundreds of hours reading and rereading all kinds of source material, receiving tutorials on technology from leading scientists, formally questioning technical experts and testing their understanding against that of various experts, examining on site the operation of the principles of the claimed invention, and deliberating over the meaning of the claim language. If district judges are not satisfied with the proofs proffered by the parties, they are not bound to a prepared record but may

> compel additional presentations or even employ their own court-appointed expert.

138 F.3d at 1478.

The Supreme Court has explained that "[t]he trial judge's major role is the determination of fact, and with experience in fulfilling that role comes expertise." *Anderson v. Bessemer City*, 470 U.S. 564, 574 (1985). The Court also reminds us that "deferential review of mixed questions of law and fact is warranted when it appears that the district court is better positioned than the appellate court to decide the issue in question or that probing appellate scrutiny will not contribute to the clarity of legal doctrine." *Salve Regina Coll. v. Russell*, 499 U.S. 225, 233 (1991); *see also Cooter*, 496 U.S. at 403 (calling for deference to the decisions of "'the judicial actor better positioned than another to decide the issue in question'" (alteration in original) (quoting *Miller*, 474 U.S. at 114)). District courts should be encouraged to resolve the factual questions bearing on claim construction and to develop a thorough record setting out their findings and the evidence supporting their conclusions. When they do, we overstep the bounds of our duty under Rule 52(a)(6) by duplicating, or ignoring, rather than deferring to that process. *Anderson*, 470 U.S. at 573; cf. *Highmark*, 701 F.3d at 1365 (Reyna, J., dissenting) (urging that we "respect[] the enduring balance between the trial judge and the appellate panel in carrying out their distinct responsibilities" by applying clear error review to trial court findings).

The concurrence downplays the extent to which we usurp the trial court's function by adherence to

Cybor by arguing both that claim construction rarely involves credibility determinations and that we are "quite as able" as district courts—or "sometimes better" able—to review the relevant documents in the record, such as the patent's prosecution history. Concurrence at 3. And the majority echoes these themes, contending that claim construction does not present questions of fact because it does not turn on credibility determinations and that leaving these questions to de novo review by our court assures greater correctness of result. The Supreme Court has made clear, however, that this narrow view of the trial court's fact-finding function is an inaccurate one. The district court's expertise is "not limited to the superiority of the trial judge's position to make determinations of credibility," but instead extends to all factual determinations. *Anderson*, 470 U.S. at 574. These determinations include findings "based on physical or documentary evidence or inference from other facts." *Id.* The Supreme Court has explained that Rule 52(a) requires deference to these findings, as well as those that turn on witness credibility. *Id.* Indeed, the Court has rejected the concurrence's reasoning with respect to Rule 52(a)(6), not only in its case law, but also through its rulemaking. In 1985, Rule 52(a) was amended, in part, because

> [s]ome courts of appeal have stated that when a trial court's findings do not rest on demeanor evidence and evaluation of a witness'[s] credibility, there is no reason to defer to the trial court's findings and the appellate court more readily can find them to be clearly erroneous. *See, e.g., Marcum v. United States*, 621 F.2d 142,

> 144-45 (5th Cir. 1980). Others go further, holding that appellate review may be had without application of the "clearly erroneous" test since the appellate court is in as good a position as the trial court to review a purely documentary record.

Fed. R. Civ. P. 52 advisory committee's note (1985) (collecting cases). The Advisory Committee continued:

> The principal argument advanced in favor of a more searching appellate review of findings by the district court based solely on documentary evidence is that the rationale of Rule 52(a) does not apply when the findings do not rest on the trial court's assessment of credibility of the witnesses but on an evaluation of documentary proof and the drawing of inferences from it, thus eliminating the need for any special deference to the trial court's findings. These considerations are outweighed by the public interest in the stability and judicial economy that would be promoted by recognizing that the trial court, not the appellate tribunal, should be the finder of facts. To permit courts of appeals to share more actively in the fact-finding function would tend to undermine the legitimacy of the district courts in the eyes of litigants, multiply appeals by encouraging appellate retrial of some factual issues, and needlessly reallocate judicial authority.

Id.

District court judges are provided training in all aspects of their duties, including claim construction

in patent litigation under *Phillips*. They then employ that training repeatedly over the years, analyzing patents, their written descriptions, and prosecution histories, receiving testimony from inventors and experts, listening to tutorials on the relevant science, and probing counsel during hearings that sometimes last days. In this case, the trial court conducted a three-day evidentiary hearing. Because *Cybor* allows us to ignore these fact-intensive inquiries by its insistence on de novo review, it not only undermines the authority of district judges, it compromises the decision-making process on appeal. Our court is given free rein to interpret claim terms, but lacks the resources to do it right. *See* Dunner & Kwon, *supra*, at 497 (noting that "the Federal Circuit, by function and design, is ill-equipped to engage in the evidentiary evaluations relevant to claim construction that are the staple of district court judges").

C.

Cybor also creates greater incentives for losing parties to appeal, thus discouraging settlements and increasing the length and cost of litigation. As Judge Rader observed in dissenting from the court's pronouncements on claim interpretation in *Cybor*, "unfettered review authority" undercuts certainty and discourages settlement. 138 F.3d at 1475. It is not until "the parties know the meaning of the claims [that] they can predict with some reliability the likelihood of a favorable judgment, factor in the economics of infringement, and arrive at a settlement to save the costs of litigation." *Id.* But under *Cybor*, "the trial court's early claim interpretation provides no early certainty at all, but

only opens the bidding. The meaning of a claim term is not certain (and the parties are not prepared to settle) until nearly the last step of the process—decision by the Court of Appeals for the Federal Circuit." *Id.* at 1476; *see also* Amicus Br. of Prof. Peter Menell at 3 (lamenting that *Cybor* "discourage[s] settlements following claim construction and trial, delay[s] resolution of patent disputes, and run[s] up the overall costs of patent litigation"); Amicus Br. of Am. Intellectual Prop. Ass'n at 8 ("*Cybor* thus fosters wasteful, expensive litigation and discourages timely settlement. That result unnecessarily ties up courts and increases expense to litigants."); Amicus Br. of Am. Bar Ass'n at 10-11 (observing that *Cybor* discourages settlement); Amicus Br. of Ass'n of Bar of N.Y. at 15-16 (same); Amicus Br. of Conn. Intellectual Prop. L. Ass'n at 13 ("Even when a case goes to trial, the losing party has very little incentive to settle disputes, since there is a significant chance that at least some material part of the trial court's decision will be reversed on appeal."); Amicus Br. of Fed'n Internationale Des Conseils en Propriete Intellectuelle at 11 (same); Amicus Br. of Paul R. Michel at 4 (same).[7]

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[7] The majority cites data showing that a declining percentage of cases proceed to trial or are appealed. *See* Maj. Op. at 35-36. According to the majority, these trends show that "the *Cybor* review procedure assists in resolving litigation before full trial or extensive discovery," thereby facilitating settlement and reducing litigation costs. *Id.* at 36. Nothing suggests that these declines can be attributed to this court's de novo review of claim construction, however. Declining trial and appeal rates can easily be attributable to other factors, including (1) the availability of parallel proceedings at the PTO and ITC where

D.

Contrary to the majority's claim, moreover, *Cybor* does not unqualifiedly promote uniformity or predictability of outcome in the patent system. As noted previously, the claim construction issues presented in patent cases are mostly fact and case specific. A claim construction decision in a given case will provide little guidance on the words used in different patents. Their resolution will do no more than declare the boundaries of a patent as between the parties in suit. *See Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found.*, 402 U.S. 313, 329-30 (1971) (observing that "[s]ome litigants—those who never appeared in a prior action—may not be collaterally estopped without litigating [an] issue"). And, there is no guarantee that panels of this court will construe like claims in a like manner, even when in the same patent. *Compare CVI/Beta Ventures, Inc. v. Custom Optical Frames, Inc.*, 92 F.3d 1203 (Fed. Cir. 1996) (affirming the determination that "greater

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decisions in those tribunals might moot further activity before the district courts, or even prevent district court judgments from becoming final, (2) increased resort to and availability of sophisticated alternative dispute resolution mechanisms, including the increased involvement of retired district court judges with patent litigation experience in such procedures, (3) improved case management practices by trial judges who have become more practiced at handling patent litigation and who now often have the benefit of detailed local rules governing the same, (4) the fact that, once this court provided clear guidance regarding claim construction in *Phillips*, trial courts were given a better roadmap for undertaking the exercise of claim construction, and (5) the increased experience and expertise of trial courts that itself may be fostering settlements. The majority reads far too much regarding the wisdom of *Cybor* into these general statistics.

than 3% elasticity" did not require "complete recovery after a strain of greater than 3%" within the meaning of claim 1 of U.S. Patent No. 4,896,955), *with CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1158 (Fed. Cir. 1997) (construing "greater than 3% elasticity" in claim 1 of U.S. Patent No. 4,896,955 as requiring complete recovery after being subjected to stress); *see also* Kimberly A. Moore, *Are District Court Judges Equipped to Resolve Patent Cases?*, 15 Harv. J.L. & Tech. 1, 18-21 (2001) (observing that "[t]he CVI/Beta cases create doubt about whether the Federal Circuit serves as a test of 'accuracy' of district court construction").

In fact, our case law expressly holds that we are not bound by claim constructions we adopt on appeal from the grant or denial of a preliminary injunction when considering the *same* claims again upon the final judgment.[8] *See Glaxo Grp. Ltd. v. Apotex, Inc.*,

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[8] It is curious that, when reserving the right to change our own claim constructions at later points in a single case, we justify that position on grounds that the greater fulsomeness of the record at the final judgment stage better informs our claim construction analysis. *Transonic Sys., Inc. v. Non-Invasive Med. Techs. Corp.*, 75 F. App'x 765, 774 (Fed. Cir. 2003) ("A district court therefore is at liberty to change the construction of a claim term as the record in a case evolves after a preliminary injunction appeal."); *Jack Guttman, Inc. v. Kopykake Enters., Inc.*, 302 F.3d 1352, 1361 (Fed. Cir. 2002) ("District courts may engage in a rolling claim construction, in which the court revisits and alters its interpretation of the terms as its understanding of the technology evolves. This is particularly true where the issues involved are complex, either due to the nature of the technology or because the meaning of the claims is unclear from the intrinsic evidence." (citation omitted)). If the trial record is effectively meaningless to the claim construction inquiry as we now hold, what more could we know about claim

376 F.3d 1339, 1346 (Fed. Cir. 2004) ("An appellate court's preliminary injunction opinion has no conclusive bearing at the trial on the merits and is not binding on a subsequent panel." (citing *Univ. of Tex. v. Camenisch*, 451 U.S. 390, 395 (1981)); *Transonic Sys., Inc. v. Non-Invasive Med. Techs. Corp.*, 75 F. App'x 765, 774 (Fed. Cir. 2003) ("We have consistently followed the Supreme Court's precedent by holding that a claim construction reached during an appeal from a grant of a preliminary injunction is tentative and is not binding on the district court in subsequent proceedings."). We, thus, do not even have an internal structure that unerringly assures uniformity.

To the limited extent uniformity might be served by de novo review, moreover, any marginal benefit from that increased uniformity is more than offset by the decreased certainty caused by making district court decisions more vulnerable to reversal. *See* Kelly Casey Mullally, *Legal (Un)Certainty, Legal Process, and Patent Law*, 43 Loy. L.A. L. Rev. 1109, 1149-50 (2010) (examining how de novo review increases one kind of certainty at the cost of "mak[ing] district court judgments less certain" by "increas[ing] the probability that the lower court's decision will be reversed"). And, as the PTO points out, "even if some marginal decrease occurred in this Court's ability to ensure perfect uniformity in the interpretation of patent claims, that decrease would not provide a reason to ignore the clear mandate of Rule 52(a)." Amicus Br. of United States at 12.

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construction later in a case than we knew when we first visited it?

We are not alone in the belief that *Cybor* does little to promote the uniformity with which the majority is now concerned. Indeed, "[i]n the government's view, recalibrating the standard of review to reflect the trial court's 'institutional advantage' in considering certain types of evidence in the claim-construction process, while preserving this Court's ability to give *de novo* review to the trial court's ultimate construction, would promote 'interjurisdictional uniformity.'" Amicus Br. of United States at 1213 (quoting *Markman*, 517 U.S. at 391). As several amici explain, there are numerous other ways to improve uniformity of claim construction scope and interpretation, including improvements to the patent prosecution process, use of post-grant review procedures, or even consolidation of cases addressing the same patents before a single trial judge through the already well-established multidistrict litigation practice. *See, e.g.*, Amicus Br. of Prof. Peter Menell at 22-24. And, as the American Bar Association notes, it is more likely that uniformity will be served by greater reliance on the claim construction decisions of the skilled fact finders—the district court judges—than by adhering to *Cybor*'s de novo standard of review. Amicus Br. at 13.

Our case law teaches that stare decisis is not an obstacle when our law causes such negative consequences. The recent decision by our en banc court in *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276 (Fed. Cir. 2011) (en banc), is a clear example of this court's willing-ness to change our law where, as here, experience proves our past decisions were unwise. In *Therasense*, this court made drastic changes to the law with the aim of making claims of

inequitable conduct more difficult to prove. *See id.* at 1290-91. In explaining why we did so, we noted that, over the years, we had "embraced reduced standards for intent and materiality to foster full disclosure to the PTO." *Id.* at 1288. But, "[t]his focus on encouraging disclosure had numerous unforeseen and unintended consequences." *Id.* Given the negative effects of our precedent, we wholly abrogated our decisions in *Orthopedic Equipment Co. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376 (Fed. Cir. 1983), *Driscoll v. Cebalo*, 731 F.2d 878 (Fed. Cir. 1984), and *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350 (Fed. Cir. 1984), and required a greater showing to demonstrate inequitable conduct. Even the dissent in *Therasense* had no problem with abrogating our body of case law on inequitable conduct, disputing only what new test should be adopted in its stead. *See Therasense*, 649 F.3d at 1302 (Bryson, J., dissenting) (urging adoption of a new standard, but one that differed from that proposed by the majority).

Likewise, in *Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp.*, 383 F.3d 1337 (Fed. Cir. 2004) (en banc), we overturned case law because we felt it had problematic effects. There, we observed that "implementation of [our prior] precedent has resulted in inappropriate burdens on the attorney-client relationship." 383 F.3d at 1343. Looking at the full range of consequences flowing from our case law, we concluded that "the conceptual underpinnings of this precedent have significantly diminished in force." *Id.* at 1344 (citation and internal quotation marks omitted). So, we changed the law. *Id.* ("The adverse inference that an opinion

was or would have been unfavorable, flowing from the infringer's failure to obtain or produce an exculpatory opinion of counsel, is no longer warranted. Precedent authorizing such inference is overruled.").

Thus, we have made clear that stare decisis does not prevent our court from changing our law where, as here, there are compelling reasons to do so.

VII.

In short, while *Markman* instructs us that claim construction presents a question for the court to resolve, it also instructs us that claim construction is a "mongrel practice," presenting a mixed question of law and fact. While we agree that the *ultimate question* of claim meaning should remain subject to de novo review, claim construction often requires district courts to resolve underlying issues of disputed fact. These include, among others: whether a claim term had a specialized meaning among those skilled in the art at the time; what texts, including treatises and dictionaries, demonstrate about how a person of skill in the art would interpret a claim term, and which contemporaneous tests are most relevant; whether to credit one expert's testimony over another's regarding issues bearing on claim construction; who qualifies as a person of ordinary skill in the art; what is the relevant field of invention; what prior art is relevant; what a person of skill in the art would glean from that prior art; and what inferences can be fairly drawn from the prosecution history, including

whether a disclaimer of claim scope has occurred.[9] When a district court makes fact-findings needed to resolve claim construction disputes, Rule 52(a) requires us to defer to those findings unless they are clearly erroneous.

Cybor ignores both the realities of claim construction and Rule 52(a)'s demands. It is time we acknowledge the limitations of our appellate function and our obligation to comply with the Federal Rules of Civil Procedure, and give trial judges the deference their expertise and efforts deserve. Stare decisis is no bar to our doing so. Nor is concern about the fact that employing the proper standard of review in this context will not always be easy. For all these reasons, I respectfully dissent.

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[9] Notably, a district court's factual determinations, even those about the historical meaning of a claim term, *will not* resolve the legal question of what construction is to be afforded a claim term. This court would be free to conclude that a claim term has a different meaning than its historically common one based on the four corners of the patent itself, or on application of legal doctrines applicable to claim construction such as claim differentiation, meanings we have subscribed to common terms (e.g., "comprising"), or the concept of an inventor being permitted to act as his own lexicographer.

REPLY BRIEF

No. 13A1003
(13-854)

IN THE SUPREME COURT OF THE UNITED STATES

TEVA PHARMACEUTICALS USA, INC., *et al.*,

Applicants,

v.

SANDOZ, INC., *et al.*,

Respondents.

On Application for Stay and On Writ of Certiorari
to the United States Court of Appeals for the Federal Circuit

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REPLY IN SUPPORT OF APPLICATION TO RECALL AND STAY THE FEDERAL CIRCUIT'S MANDATE

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April 17, 2014

RULE 29.6 STATEMENT

The Rule 29.6 statement included in Teva's application remains accurate.

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REPLY IN SUPPORT OF APPLICATION TO RECALL AND STAY THE FEDERAL CIRCUIT'S MANDATE

INTRODUCTION

The District Court in this case entered an injunction barring respondents from infringing Teva's '808 patent until it expires September 1, 2015. Respondents never disputed that their launch of an infringing product, anytime during that period, would cause Teva irreparable injury. They never sought a stay of that injunction. And the only reason why that injunction will now expire May 24, 2014, is that the Federal Circuit prematurely issued a mandate declaring the '808 patent invalid. The court of appeals did so only because it reviewed *de novo* and second-guessed the District Court's factual findings. This Court will now decide whether the Federal Circuit erred, and should instead have reviewed the factual findings deferentially as Fed. R. Civ. P. 52(a)(6) requires. But respondents conspicuously do not deny that during the window before this Court's decision, they intend to launch their infringing products immediately if they secure FDA approval, inflicting the very irreparable harm the District Court originally enjoined. This Court should recall and stay the Federal Circuit's mandate, "thereby effectively reviving" the District Court's judgment and injunction as they stood before the Federal Circuit issued its reversal. *Norman v. Reed*, 502 U.S. 279, 287 (1992).

Respondents latch onto the District Court's purely ministerial order conforming its injunction to the terms of the Federal Circuit's mandate. The District Court's original permanent injunction is gone, they say, and Teva must satisfy the standard to get a new injunction from scratch—as if Teva were in the

same position as a litigant who has *failed* to obtain an injunction at every level of the federal judicial system and finally seeks an injunction from the Circuit Justice. That is nonsense. Teva *secured* an injunction, and the only thing that affected that injunction is the Federal Circuit's mandate—the same mandate that is under this Court's review and will likely be reversed.

What Teva needs is a stay of that mandate, and it amply meets the relevant standard. There plainly is at least a "fair probability" that this Court will reverse. The grant of certiorari is powerful evidence by itself; the point is confirmed by the extensive criticism the Federal Circuit's no-deference rule has drawn from the United States, scholars, practitioners, and even many Federal Circuit judges. Indeed, while the stay standard looks only to success *in this Court*, Teva is likely to succeed *fully*: under the correct standard of review, respondents cannot overcome the District Court's findings and their indefiniteness defense cannot prevail.

The irreparable-harm calculus has not changed since the District Court entered the permanent injunction: both then and now, the launch of an infringing generic during the term of the '808 patent would cause Teva irreparable injury. Respondents' harm arguments are premised entirely on the Federal Circuit's flawed finding that Teva's patent is invalid, but the law is clear: in assessing irreparable harm, this Court presumes that *Teva* is correct on the merits. With the proper understanding—that the Federal Circuit erred in invalidating the '808 patent—the balance of hardships and the public interest overwhelmingly support restoring the injunction until this Court decides the merits.

ARGUMENT

I. This is an application for a stay of mandate, not an injunction.

The relief Teva seeks is simple: the Federal Circuit's decision should not remain in effect, and disrupt the District Court's permanent injunction, while this Court reviews whether the Federal Circuit's decision rests on a fundamentally wrong foundation—*de novo* review rather than deference. The stay Teva seeks is identical in every material way to the stays of mandate pending certiorari review that courts of appeals routinely grant, dozens of times a year, under Fed. R. App. P. 41(d)(2). The fact that in this case the court of appeals issued the mandate, minutes after denying a stay and before this Court could consider the matter, does not change the standard, *see* Stay Appl. 8, a point that respondents have conceded. *See* 13A458 Stay Opp. 9 (reciting the stay standard).

Yet respondents now contend that what Teva is really seeking is an injunction, not a stay, and that Teva must therefore meet a higher standard.[1] That contention misunderstands the difference between a stay and an injunction. "A stay simply suspends judicial alteration of the status quo, while injunctive relief grants judicial intervention that has been withheld by lower courts." *Nken v. Holder*, 556 U.S. 418, 429 (2009) (citations and brackets omitted). Teva is not seeking something "that has been withheld by lower courts" at all; it is seeking to

[1] Respondents also offer a cursory assertion (Stay Opp. 15) that Teva's burden should be higher because it did not proceed first in the court of appeals. But respondents offer no response at all to Teva's discussion of why the Federal Circuit very likely lacks authority to grant any such relief. Stay Appl. 17-19. Respondents thus miss the point: Teva should not be held to a higher standard merely because it has proceeded in *the one court with clear authority to grant relief* following the grant of certiorari. Teva reiterates (*see id.* at 19) that it will proceed expeditiously in the Federal Circuit if this Court or the Circuit Justice directs Teva to do so after clarifying that the Federal Circuit may grant Teva relief notwithstanding this Court's having taken the case on certiorari.

reinstate the original injunction that the District Court issued, by asking this Court to "suspend[]" the Federal Circuit's "alteration of the status quo." *Id.* Even under the Federal Circuit's mandate, a permanent injunction is in force today. That injunction can and should remain in force past May 24, 2014, as the District Court originally specified—so long as the Federal Circuit's mandate is stayed.

Put another way, Teva is not asking *this* Court to enjoin respondents from infringing the '808 patent, any more than Maryland was asking this Court to convict Alonzo King. *See Maryland v. King*, 133 S. Ct. 1 (2012) (Roberts, C.J., in chambers) (staying mandate of appellate court that reversed King's criminal conviction). The District Court in this case enjoined respondents from such infringement, and the requested stay would prevent the Federal Circuit's incorrect decision from disrupting that injunction while this Court decides whether (as is likely) the Federal Circuit must be reversed. *See, e.g., U.S. Postal Serv. v. Nat'l Ass'n of Letter Carriers*, 481 U.S. 1301, 1301-02 (1987) (Rehnquist, C.J., in chambers). In *Letter Carriers*, the Postal Service had sued in district court and won an order precluding reinstatement of a letter carrier who had been convicted of delaying the mail (as an arbitrator had ordered). The D.C. Circuit reversed, but the Circuit Justice—applying the stay standard, not the injunction standard—stayed that mandate to permit "[c]ontinuation of the status quo," *i.e.*, the District Court's order granting the Postal Service relief. *Id.* at 1302-03. Although the effect of this Court's order was to continue the restraint precluding the felonious postal worker from being reinstated, this Court's order was a stay, not an injunction.

Respondents cite a host of cases applying the injunction standard. But in those cases, unlike this one, injunctive relief had been "withheld by lower courts." *Nken*, 556 U.S. at 429.[2] Respondents contend that this case moved into that category the moment the District Court undertook the routine act of conforming its injunction to the Federal Circuit's mandate. That argument ignores the sole reason *why* the District Court modified the injunction: the Federal Circuit had issued its mandate and required the District Court to treat the '808 patent as invalid. And the '808 patent was the only patent protected by the injunction beyond May 24, 2014. Accordingly, when the mandate issued, the District Court had no choice but it had to modify the injunction so that it no longer protected the '808 patent. *See, e.g.*, *Briggs v. Pa. R.R. Co.*, 334 U.S. 304, 306 (1948).[3] For that reason, the parties agreed upon a modification "in light of the Federal Circuit mandate." Unopposed Mot. to Enter J. Pursuant to L. Civ. R. 58.1, at 2, ECF No. 270, No. 1:09-cv-08824-WHP (S.D.N.Y. filed Dec. 16, 2013). Teva did not oppose and, indeed, *could not* have opposed the modification because "the form of judgment accurately reflect[ed] the mandate from the Federal Circuit." *Id.*

A ministerial, nondiscretionary act by the District Court, obeying the court of

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[2] *See Hobby Lobby Stores, Inc. v. Sebelius*, 133 S. Ct. 641, 642 (2012) (Sotomayor, J., in chambers); *Lux v. Rodrigues*, 131 S. Ct. 5, 6 (2010) (Roberts, C.J., in chambers); *Turner Broad. Sys., Inc. v. FCC*, 507 U.S. 1301, 1301 (1993) (Rehnquist, C.J., in chambers); *Ohio Citizens for Responsible Energy, Inc. v. NRC*, 479 U.S. 1312, 1312 (1986) (Scalia, J., in chambers).

[3] Although the Federal Circuit dropped a footnote suggesting that the District Court should consider whether modification of the injunction was necessary, that was because the Federal Circuit evidently did not realize that the '808 patent (which is not listed in the "Orange Book") expired later than the other patents. Pet. App. 24a n.5 ("We note that, according to the Orange Book, all of Teva's Copaxone® patents expire on the same date: May 24, 2014. We remand for the district court to determine whether there exists any need to modify its injunction."). The mandate to implement the decision invalidating the '808 patent left the District Court with no choice.

appeals, cannot fundamentally alter the standard that Teva must meet *in this Court*. The combined actions of the Federal Circuit (issuing its mandate) and the District Court (obeying it) do not wipe the slate clean and require Teva to submit new proofs to this Court as if Teva had never had an injunction—any more than the modification moots the appeal from the original order, *see United States v. Villamonte-Marquez*, 462 U.S. 579, 581 n.2 (1983); *Aetna Cas. & Surety Co. v. Flowers*, 330 U.S. 464, 467 (1947). If this Court stays the Federal Circuit's mandate while considering the merits, the relief the court of appeals awarded respondents will be put on hold, the '808 patent will no longer be treated as invalid, and the modification of the injunction will no longer be appropriate. In short, a stay should be sufficient to "reviv[e]" the District Court's original injunction. *Norman*, 502 U.S. at 287.[4] Even if it were not, the stay certainly would "remove the barrier" to the District Court's undoing the ministerial act it undertook to comply with the mandate, and reinstating its original injunction. *Graddick v. Newman*, 453 U.S. 928, 944 (1981) (opinion of Rehnquist, J.).

That is particularly true where the status quo has not yet changed. The District Court's modification of the injunction has no effect until May 24, 2014, and respondents do not claim that anyone has taken any action in supposed reliance on the modification. This case is therefore completely different from *Graddick*, in which the disagreement between Justice Powell (whose solo opinion respondents

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[4] In *Norman*, the lower courts had reversed the decision of an administrative agency. The Circuit Justice ordered the mandate "stayed or, if necessary, recalled," and this Court continued the stay pending certiorari. 502 U.S. at 287. As this Court later described, its order staying the mandate "thereby effectively reviv[ed] the [agency's] decision." *Id.*

cite) and then-Justice Rehnquist was over whether a writ of habeas corpus could still be stayed weeks after it had been executed and more than 200 prisoners released. *Compare id.* at 936 (opinion of Powell, J.) (suggesting "that an order, once executed, cannot be 'stayed'"), *with id.* at 943-44 (opinion of Rehnquist, J.) (opining that the habeas writ could still be stayed because it had continuing effects). Whatever the correct answer to that question of habeas practice, it is clear that *this* order has not been "executed" and has had no effect on the parties' conduct. "Affirmative action" is not "necessary to restore the status quo," *id.* at 936 (opinion of Powell, J.), precisely because the disruption to the status quo comes only from the Federal Circuit's mandate, which has not yet had any real-world effect. All that is necessary is to recall that mandate and permit the reinstatement of the District Court's permanent injunction.

II. Teva has amply demonstrated a fair prospect that this Court will reverse the Federal Circuit.

Respondents accuse Teva of "simply assum[ing]" or perhaps "assert[ing]" that the grant of certiorari establishes the likelihood of success. Stay Opp. 15-16. In fact, Teva discussed its likelihood of success at length, Stay Appl. 10-12, and demonstrated more than the requisite "fair prospect that the Court will reverse the decision below," *King*, 133 S. Ct. at 2 (Roberts, C.J., in chambers) (citation omitted). Respondents suggest that Teva must show that it will *also* succeed in some other forum, *e.g.*, on remand. This Court has never required any such showing of future success, but in any event Teva has amply demonstrated that reversing the Federal Circuit's error will also reverse the outcome.

A. The no-deference rule is ripe for reversal.

Respondents contend that they "may well" win on the merits. Stay Opp. 17. That bears no resemblance to the actual stay standard, which is whether there is a "fair prospect" that this Court will reverse. *King*, 133 S. Ct. at 2.

The grant of certiorari in a patent case from the Federal Circuit is itself powerful evidence that there is a "fair prospect" that this Court will set aside the Federal Circuit's ruling. This Court is not likely to invest its time reviewing a Federal Circuit patent case between private parties if there were not even a reasonable prospect that the Court would reverse.

But in this case there is far more: for instance, the briefs of the United States and a host of other *amici*, the closely divided *en banc* court (6–4), and two decades of vigorous dissents from Federal Circuit judges seeking to overturn the no-deference rule all demonstrate not just a fair prospect, but a probability of reversal. Stay Appl. 10-11. Indeed, the outcome in *Lighting Ballast* rests on the vote of a judge who, *as respondents emphasized at the certiorari stage*, was one "of the most vocal judges calling for a deferential standard of review of claim-construction rulings." Br. in Opp. 26; *see* Stay Appl. 11. Judge Moore set aside her conviction that the Federal Circuit's no-deference rule is wrong, based on *stare decisis*. But *stare decisis* does not require this Court to follow Federal Circuit precedent, and respondents do not rely on it.

Rather, respondents offer two halfhearted paragraphs on the merits. Stay Opp. 16-17. These paragraphs represent the first time respondents have actually joined issue on the merits of the Federal Circuit's no-deference rule. *See* Cert. Reply

1 (noting that respondents had written a 30-page opposition to certiorari without a word on the merits). If respondents really thought this Court had already squarely answered the question presented here, in a decision as recent as *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), they certainly would have said so in their brief in opposition. They did not. And *Markman* reserved the question presented here; it did not decide it.[5] Ultimately, the most that respondents can say is that the Court "may well" answer the question presented their way. Stay Opp. 17. That is not the standard for opposing a stay. Rather, to prevail on likelihood-of-success grounds, respondents would have to show that this Court *almost certainly* will answer the question presented their way (*i.e.*, that there is not even a reasonable possibility that Teva will prevail). They cannot make any such showing.

Nor do respondents gain any ground by recycling, almost word for word, the section of their brief in opposition in which they contended that this case was a poor vehicle to decide the question presented. *Compare* Br. in Opp. 19-21 *with* Stay Opp. 18-19. This Court has already rejected such considerations by granting certiorari. And even if it had not, respondents' repeated emphasis on Figure 1 of the patent (Stay Opp. 7-8, 19) is telling. Both Teva's expert and the District Court explained why a skilled artisan would understand that figure not to support respondents' position. Those are matters of historical scientific fact—how is a graph like that depicted in the figure generated, and what is the expected effect of the data

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[5] This Court held in *Markman* that the Seventh Amendment did not require submission of claim construction to the jury, but stated that it was *not* deciding whether its conclusion "crystallized a law/fact distinction." 517 U.S. at 384 n.10. The application of Rule 52(a)(6) turns on precisely that distinction. This case presents the question that this Court expressly declined to reach in *Markman*.

conversion necessary to generate the figure?—and thus are properly the subject of factual findings. Respondents offered no contrary evidence; they simply convinced the Federal Circuit to interpret the graph in exactly the way the District Court found would be scientifically incorrect, without ever impeaching the District Court's findings. Teva explained as much at the certiorari stage. Cert. Reply 3-4. It is telling that instead of responding to this point, respondents just deny once again that any scientific facts bore on the interpretation of this patent.

B. The analysis ends with a "fair prospect that [this] Court will . . . reverse the decision below."

Respondents devote much of their discussion of the merits to asserting that the Federal Circuit will eventually reinstate its "invalidity judgment" *even if* this Court reverses the Federal Circuit's decision. That prediction is flawed on its merits, as discussed below. *See* Section II.C, *infra*. But as a threshold matter, *future* proceedings are irrelevant: a stay lasts only while the case is pending in this Court, and so a stay applicant need establish only a fair prospect of success *in this Court*, as decades of opinions confirm.

This Court has consistently described likelihood of success as "'a fair prospect' that the Court will *reverse the decision below*." *King*, 133 S. Ct. at 2 (emphasis added) (quoting *Conkright v. Frommert*, 556 U.S. 1401, 1402 (2009) (Ginsburg, J., in chambers)). The analysis stops with the fair prospect of reversal. *Accord, e.g.*, *John Doe Agency v. John Doe Corp.*, 488 U.S. 1306, 1308 (1989) (Marshall, J., in chambers) (stating that a Circuit Justice must attempt to predict "the final outcome of the case *in this Court*") (emphasis added). That is why this Court has from time

to time described the test as whether "at least five Justices" will ultimately decide the question presented to this Court in favor of the stay applicant. *Araneta v. United States*, 478 U.S. 1301, 1304 (1986) (Burger, C.J., in chambers); *accord, e.g.*, *Conkright*, 556 U.S. at 1401 (requiring "a fair prospect that a majority of th[is] Court will conclude that the decision below was erroneous"); *Rostker v. Goldberg*, 448 U.S. 1306, 1308 (1980) (Brennan, J., in chambers) (same).[6] The Circuit Justice need not *also* predict how a panel of circuit judges, or a district judge, or a jury might later decide the case once the case is remanded—particularly where, as here, that future decision may turn on issues outside the question presented to this Court. *See, e.g.*, *Nat'l Farmers Union Ins. Co. v. Crow Tribe of Indians*, 468 U.S. 1315, 1315-16, 1321 (1984) (Rehnquist, J., in chambers) (granting a stay based in part on the "reasonable probability for at least partial success on the merits" of a justiciability issue, while expressing "no opinion" about whether, if this Court reversed the court of appeals' holding of nonjusticiability, "applicants would necessarily prevail" on the merits).

The question presented here is whether the Federal Circuit erred by reviewing factual findings *de novo*. Pet. i. In ruling on the stay application, the Court need "express no opinion" about the ultimate merits of respondents' patent-invalidity argument. *Nat'l Farmers*, 468 U.S. at 1321. What matters is that Teva has shown a "sufficient likelihood that the court below erred in one or more important respects." *NCAA v. Board of Regents*, 463 U.S. 1311, 1313-14 (1983)

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[6] The same is true when a court of appeals stays a district court's ruling. The question is not whether the appellant will ultimately prevail—*e.g.*, at trial; the question is the "likelihood of success *on appeal*." *Hilton v. Braunskill*, 481 U.S. 770, 778 (1987) (emphasis added).

(White, J., in chambers).

Respondents also make the equally unpersuasive suggestion (Stay Opp. 13 n.3) that the Court might affirm on the ground that the patent is indefinite anyway, under any change to the indefiniteness standard that the Court might announce in *Nautilus, Inc. v. Biosig Instruments, Inc.*, No. 13-369. But as respondents themselves have emphasized, any revision of the substantive indefiniteness standard is "not relevant to the question presented" here.[7]

C. Teva has far more than a "fair prospect" of ultimately prevailing on clear-error review

Even if the stay analysis, or the question presented, encompassed whether the District Court's factual findings would survive clear-error review, respondents still could not show that those findings were so deficient that Teva has no "fair prospect" of prevailing. As Teva has explained throughout these proceedings, the standard of review was outcome-determinative. Pet. 24-27; Cert. Reply 2-5. Respondents' invalidity defense required them to convince the court, by clear and convincing evidence, that the '808 patent was so ambiguous that even a highly trained chemist familiar with peptide synthesis could not decipher the meaning of "average molecular weight." The District Court found that such a highly skilled artisan *would* know the meaning of the disputed term. The court's findings are not clearly erroneous, and they defeat the invalidity claim.

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[7] Br. in Opp. 27-28 (asserting that "the underlying substantive issue of what standard of indefiniteness should be applied . . . is not relevant to the question presented as framed by Teva"). Teva urged the Court to hold for *Nautilus* because that case may shed light on a different point, *i.e.*, whether claim construction for indefiniteness purposes entails factual issues. Pet. 32-35; Cert. Reply 8-11. This Court's decision on *that* point could only help Teva, since the Federal Circuit holds that there are no factual issues in claim construction. Pet. 4-6.

Respondents simply mischaracterize Dr. Grant's testimony in asserting that he "opined that Figure 1 [of the patent specification] was erroneous." Stay Opp. 22. Rather, Dr. Grant explained how to *read* Figure 1, from the perspective of a scientist familiar with interpreting chromatography results. And he explained why the inference respondents sought, and that the court of appeals later drew—that Figure 1 is inconsistent with the use of peak average molecular weight—was simply wrong. Respondents put in no contrary evidence and have never given any reason why the District Court's findings crediting Dr. Grant were incorrect, much less clearly erroneous. And if the District Court's findings were right, the Federal Circuit's own lay reading of the patent was wrong, and the patent is not indefinite.[8]

III. As the District Court's injunction reflected, respondents' contemplated launch of infringing products threatens irreparable harm, which justifies recalling the mandate and reinstating the injunction.

A. Respondents never disputed below that the District Court's permanent injunction protects Teva against irreparable harm.

Respondents never argued below that Teva would face no irreparable harm if they are permitted to launch their generic copolymer-1 products before the expiration of the '808 patent. They made no effort, and certainly made no record, to support such a contention in the District Court, and the District Court entered a permanent injunction. Respondents then made no attempt whatever to persuade

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[8] Respondents' reference to Teva's pursuit of a reissue patent (Stay Opp. 10-11) is altogether irrelevant here. In unsuccessfully *seeking* a reissue patent—which the patent examiner has since denied—Teva stated after the Federal Circuit's mandate issued that the patent was invalid for indefiniteness. That statement was and is legally correct, because the Federal Circuit has put its decision into effect; however, recalling the mandate (or reversing the Federal Circuit) would change the patent's status, and Teva would update the oath as appropriate. Any innuendo that Teva misled the Patent Office is unfounded: Teva has kept the Patent Office fully informed of the filing and content of its previous stay application and certiorari papers.

the Federal Circuit that the District Court erred in granting injunctive relief. Teva now seeks a stay to restore that very injunction and to prevent the very same irreparable harm—the launch of an infringing product.

Respondents now insist that before issuing a stay to restore the injunction, the Circuit Justice should assume the mantle of a trial judge and consider evidence about the effect of a generic launch on the market for copolymer-1 treatments for multiple sclerosis, without the benefit of any discussion or analysis by the lower courts.[9] There is no warrant for such a demand. Respondents acknowledge that the only thing that has changed since they accepted injunctive relief without complaint is that the Federal Circuit ruled on their appeal. Stay Opp. 24-25. But that ruling carries no weight in the stay analysis, because this Court assesses irreparable harm "assuming [Teva's] position on the merits is correct." *E.g.*, *Philip Morris USA Inc. v. Scott*, 131 S. Ct. 1, 3 (2010) (Scalia, J., in chambers); *see* Stay Appl. 8, 12.

Nor does the fact that the District Court was compelled by the Federal Circuit's mandate to modify its permanent injunction reopen that court's earlier finding of irreparable harm. *Contra* Stay Opp. 25. On remand from the Federal Circuit, the District Court certainly did not conclude that irreparable harm exists only until May 24, 2014, and not thereafter. It did not weigh irreparable harm on

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[9] Respondents suggest that Teva "implicitly acknowledged" that this Court should revisit irreparable harm in connection with its application to recall the mandate by submitting the Declaration of John Hassler. But Teva stated clearly in its application that irreparable harm was established below without objection from respondents and that it was too late for them to raise an objection in this Court. Stay Appl. 13. The Hassler Declaration was submitted because, in their previous stay opposition, respondents asserted for the first time (and cursorily) that Teva would face no irreparable harm. *Id.* at 14 n.3. Teva accordingly submitted the declaration to confirm that this case is similar to many other cases, cited in Teva's application, that found irreparable harm sufficient to support an injunction against generic launch before patent expiration.

remand *at all*. It simply did what was required by the Federal Circuit's mandate.

B. Respondents' arguments do not undermine the District Court's determination of irreparable harm

Respondents do not dispute that courts routinely conclude that pharmaceutical company patentees face irreparable harm from the launch of infringing generic drug products. *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1361-62 (Fed. Cir. 2008); Stay Appl. 13 (citing cases). *See generally eBay Inc. v. MercExchange, LLC*, 547 U.S. 388, 395 (2006) (Roberts, C.J., concurring) ("[C]ourts have granted injunctive relief upon a finding of infringement in the vast majority of patent cases."). Nor do respondents deny that the intangible harms that will result from reduced patient services and the layoff of experienced personnel who support such services, *see* Stay Appl. 14, are commonly found irreparable as well. *See, e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382-83 (Fed. Cir. 2006). The only contrary case respondents cite is *Eli Lilly & Co. v. American Cyanamid Co.*, 82 F.3d 1568, 1578-79 (Fed. Cir. 1996). That decision merely considered whether a district court committed clear error in denying a preliminary injunction because, "under the specific circumstances of this case," the patentee would not face irreparable harm during the pendency of the litigation. *Id.* at 1578. The Federal Circuit reviewed that finding deferentially and found no "clear error." *Id.* Here, of course, the District Court found irreparable harm and entered a permanent injunction.

Respondents seek to score rhetorical points by pointing out that as a defendant, Teva has attempted to "refute" similar claims of irreparable harm. The argument that "Teva was right then" (Stay Opp. 26) is curious coming from

respondents, who have *successfully* argued that they would suffer irreparable harm if their competitors are not enjoined from launching generic products prior to the expiry of respondents' patents.[10] In that case, the district court credited Momenta's and Sandoz's assertions and found irreparable harm based on their arguments that such "harm would likely involve price erosion, lost market share, loss of market capitalization, reputational injury and threats to both the funding of ongoing research development and the hiring and retention of critical scientific talent." *Momenta Pharms., Inc. v. AmphaStar Pharms, Inc.*, 882 F Supp. 2d 184, 197 (D. Mass. 2011), *rev'd on other grounds*, 686 F.3d 1348, 1361 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 2854 (2013). By contrast, Teva's argument was *unsuccessful* in the case respondents cite; the district court concluded (in line with the decisions cited above) that Teva's launch of a generic drug *would* cause irreparable injury. *Eisai Co. Ltd. v. Teva Pharms. USA, Inc.*, No. 05-cv-5727, 2008 U.S. Dist. LEXIS 33747 (D.N.J. Mar. 28, 2008). That past litigation in no way refutes the irreparable injury to Teva in *this* case.

Respondents' suggestion that Teva's "delay" in filing its cert petition undermines its allegations of irreparable harm similarly makes no sense, especially coming from respondents. Teva sought a stay at the earliest opportunity following denial of rehearing and issuance of the mandate. No. 13A458. Respondents

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[10] *See* Momenta & Sandoz Mem. in Supp. of Mot. for Expedited Discovery at 3, *Momenta Pharms., Inc. v. AmphaStar Pharms, Inc.*, ECF No. 20, No. 11-cv-11681-NMG (D. Mass. filed Sept. 30, 2011) ("If Defendants are allowed to launch their infringing product, ... it will have an immediate and permanent impact on the enoxaparin market, resulting in substantial price erosion and loss of market share. Even if Defendants were subsequently removed from the market, it is uncertain whether Sandoz could ever recover the lost pricing power and there is no way to calculate the impact of customer goodwill of Sandoz attempts to raise prices.").

opposed both the stay request and certiorari as premature, arguing that the issue was unripe until the Federal Circuit decided the *Lighting Ballast* case. And they filed their opposition to certiorari weeks early, hoping that the petition would be considered—and denied—before the Federal Circuit decided *Lighting Ballast* and made the issue undeniably ripe. Their gambit nearly worked, but not quite: *Lighting Ballast* was decided on February 21, 2014, only two weeks before the Court first considered the petition at conference. Teva can hardly be said to have filed its petition too *late*; it narrowly avoided filing too *early* to obtain review. And once this Court granted review, Teva renewed its application within days.

C. Neither the countervailing harms posited by respondents nor the public interest warrants denial of the application.

Respondents complain that recalling and staying the mandate would deprive them of the opportunity to compete with Teva during part of the '808 patent's remaining term. But if the Federal Circuit had not improperly substituted its judgment for the District Court's, respondents would still be permanently enjoined from launching until September 2015. If this Court hears argument early next Term, it will be in a position to decide this case in late 2014 or early 2015.

Respondents' argument seems to be that if they could launch before this Court decides the case, they could lock up more customers who have not yet tried Teva's new three-times-per-week Copaxone® product. That product is now FDA-approved, is as efficacious as the daily injection, and allows patients to substantially reduce the number of injections they must undergo. Respondents hope that insurance companies will decide to reimburse patients only for the less expensive

(but still expensive) generic daily injection product. Respondents' desire to lock up customers before they try Teva's three-times-a-week product rests on speculation about voluntary choices between products that patients and doctors will make.[11] Such speculative fear of competition is not cognizable harm in any event.

If anything, the existence of three-times-a-week Copaxone® undermines *respondents'* position. Respondents oppose reinstating the District Court's injunction precisely so that they can undermine Teva's ability to sell the new product—one that offers real advantages to patients—and permanently erode the price of that product as well. What respondents seek to preserve is their chance to *increase* the irreparable harm that the launch of their generic products before the expiration of the '808 patent would cause Teva. Such changes in the market would make the damages from the launch of an infringing generic product even *more* difficult to calculate here than in other cases in which courts have routinely found that launching a generic product would create irreparable harm.

Respondents also repeat their bald assertion that the introduction of cheaper generic drugs inevitably serves the public interest. As Teva demonstrated in the application, Congress placed equal emphasis on giving pharmaceutical patentees the full economic benefit of their patents, recognizing that truncating that benefit would result in the development of fewer life and health saving drugs. Stay Appl.

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[11] The various newspaper and internet articles cited by Respondents are no more than the speculation of analysts and others about what percentage of patients will switch to this new formulation. Respondents fail to note that these discussions in the popular press all assume that generic entry will be possible as of May 24, 2014. In other words, contrary to the point Respondents are attempting to make, these articles merely demonstrate that the advantages of the three times per week formulation will encourage patients to switch *even if the generics are able to launch on May 24, 2014*. They do not establish any harm to respondents if the District Court's original injunction, through September 1, 2015, is restored by recalling the Federal Circuit's mandate.

17. Respondents do not dispute this, but say only that the '808 patent is invalid and invalid patents should not delay generic launch.

But this response, like respondents' entire opposition, begs the question. The District Court found that respondents had *not* proved the '808 patent to be invalid. The Federal Circuit erroneously substituted its findings for those of the District Court. And under a clear-error standard, that decision cannot stand.

D. Respondents do not substantiate any need for a bond, much less one of the magnitude they demand.

Respondents' new request for the imposition of a bond, if the Federal Circuit's mandate is stayed or recalled, is misguided. Bonds are sometimes required for preliminary injunctions, and for orders granting or staying injunctions pending appeal. But as discussed above, that is not what Teva seeks. Teva seeks an order from this Court directing the recall of the Federal Circuit's mandate and *reinstatement* of the District Court's *permanent* injunction. Had the Federal Circuit not erroneously substituted its judgment for that of the District Court, that permanent injunction—which respondents never sought to stay, and against which they never sought a bond—would still restrain respondents from launching their infringing products even after May 24, 2014. Teva has demonstrated that this Court is likely to reject the Federal Circuit's approach. Under these circumstances, no bond should be required simply to reinstate a permanent injunction that itself had no bond attached.

If the Court determines that some sort of bond is necessary, Teva is prepared to post one, as discussed further below. But this Court need not waste time

analyzing in detail the declarations submitted under seal by respondents. Rather than undertake a complex fact-finding process itself, if this Court requires a bond it can and should authorize the District Court to determine what amount would suffice. *See, e.g.*, *California v. Am. Stores Co.*, 492 U.S. 1301 (1989) (O'Connor, J., in chambers) ("This order is conditioned upon the posting of a good and sufficient bond with the Clerk of the United States District Court for the Central District of California, the adequacy of such bond to be determined by that Court."); *Becker v. United States*, 451 U.S. 1306 (1981) (Rehnquist, J., in chambers) (similar).[12]

This course is particularly warranted because the record before this Court provides no basis for determining what amount would fairly compensate respondents if this Court affirms the Federal Circuit's decision.[13] Respondents' declarations contain no more than speculative assertions, with little explanation and no supporting facts—plainly insufficient to carry respondents' burden to establish the appropriate size of any bond. *See, e.g.*, *Int'l Equity Investments, Inc. v. Opportunity Equity Partners Ltd.*, 441 F. Supp. 2d 552, 566 (S.D.N.Y. 2006) ("In fixing the amount of security required, a court is not required to order security in respect of claimed economic damages that are no more than speculative."). Trial courts exercising their discretion under Fed. R. Civ. P. 65 in imposing bonds in

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[12] *See also Leegin Creative Leather Prods., Inc. v. PSKS, Inc.*, No. 06A179 (Aug. 22, 2006) (Scalia, J., in chambers) (order recalling and staying the Fifth Circuit's mandate "conditioned upon the posting of a good and sufficient bond with the Clerk of the ... Fifth Circuit, the adequacy of such bond to be determined by that Court").

[13] Because the purpose of the bond would be to secure respondents against the (unlikely) possibility that Teva will not in fact prevail in this Court on the question presented, a payment obligation under the bond would be triggered only by this Court's affirming the judgment of the Federal Circuit and respondents' proving damages attributable to the delay between the date of FDA approval and the date of this Court's judgment.

connection with preliminary injunctions are certainly not required to accept the enjoined party's unsupported word as to the appropriate amount of the bond. *See, e.g.*, *Sanofi-Synthelabo*, 470 F.3d at 1384-85; *Celsis in Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 931 (Fed. Cir. 2012). Nor should this Court.

In a full evidentiary hearing before the District Court, Teva would demonstrate that the bond amount respondents seek is unjustifiably high. For example, Mylan, in the Tighe Declaration, includes unsupported assumptions concerning the size of the market, the percentage of the market that will shift to Mylan's product, and future harm extending many years past patent expiration. But Mr. Tighe presents no basis for any *ipse dixit* in his declaration. And Mylan's "evidence" in this regard is substantially more detailed than that provided by either Sandoz or Momenta, which offer nothing more than bald assertions of what profits they would lose over a lengthy period.

Significantly, each respondent's speculation contradicts the other's. Each respondent makes at least one key assumption that, if true, would mean the other respondent's assumption is not true. They cannot both be correct. *Compare, e.g.*, Butera Decl. ¶¶ 6 (second sentence), 11 (third sentence) *with* Tighe Decl. ¶ 6(1). Respondents' suggestion to combine their bond figures (Stay Opp. 34 n.7) therefore would entail significant double-counting even if their figures were reliable, which they are not. The conclusions reached by each respondent as to the profits that a generic product will generate between May 24, 2014 and September 1, 2015—products assumed to be equivalent, over the identical time period—are staggeringly

different. *Compare* Butera Decl. ¶ 6 *with* Tighe Decl. ¶ 8. Their numbers simply cannot be reconciled. Unsubstantiated speculation, submitted in sealed newly filed in this Court, cannot establish the appropriate size of any bond now.

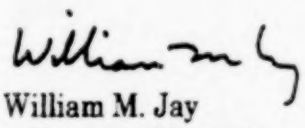
Moreover, both sets of numbers rest on the assumption that respondents will have received FDA approval by May 24, 2014. That may not occur. And the longer the FDA withholds approval after May 24, the smaller the "harm" that would be attributable to the reinstatement of the injunction—and thus the smaller an adequate bond could be.

Respondents have demonstrated neither the need for a bond nor the appropriate amount of any bond, and the latter is inherently speculative because neither the timing of FDA approval nor the number of generic products that will launch can be known at this juncture. But if this Court concludes both that it must condition an order recalling the Federal Circuit's mandate on Teva's posting a bond *and* that this Court must itself set a figure (rather than leave it to the District Court), Teva is prepared to comply. If a bond is ordered, Teva is prepared to post a bond of up to $500 million at the earliest practicable time, but in no event later than May 24, 2014. The District Court should be authorized to consider whether any additional security is required or whether a lower amount could adequately secure respondents. Until the District Court rules, Teva's proposed bond would fully protect both respondents for many months of sales even under their most wildly optimistic projections. *See* Stay Opp. 35 (claiming harm in the "hundreds of millions of dollars").

CONCLUSION

For the foregoing reasons and those stated in the application, the mandate of the Federal Circuit should be recalled and stayed until the sending down of this Court's judgment in No. 13-854, thus requiring the District Court to restore the original injunction in force before the mandate issued.

Respectfully submitted.



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April 17, 2014

JOINT APPENDIX

No. 13-854

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

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08/02/12	2	Note to file: 12-1568, 12-1569, 12-1570 (appeals started 08/02/2012) are consolidated with 12-1567. [19786]
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02/15/13	80	BRIEF FILED for Appellees Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc. and Yeda Research and Development Co., Ltd. [79]. Title: Brief of Plaintiff Appellees, [Non-Confidential version only]. Number of Pages: 86. Service: 02/15/2013 by email. Pursuant to ECF-10, filer is directed to file six copies of the brief in paper format.. [51581]
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		03/04/2013 by email. Pursuant to ECF-10, filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 03/12/2013. [56278]
03/04/13	87	BRIEF FILED for Appellants Mylan Inc., Mylan Pharmaceuticals Inc. and Natco Pharma Ltd. [83]. Title: Reply Brief of Defendants-Appellants Mylan Pharmaceuticals Inc., Mylan Inc. and Natco Pharma Ltd., [Non-Confidential version only]. Number of Pages: 30. Service: 03/04/2013 by email. Pursuant to ECF-10, filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 03/12/2013. [56282]
03/13/13	101	APPENDIX FILED for Momenta Pharmaceuticals Inc., Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd., Sandoz, Inc. and Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc. and Yeda Research and Development Co., Ltd. [99], [98], [97], [96], [95], [94], [93], [92], [91], [90]. Title: Joint Appendix, [Confidential and Non-Confidential versions]. Number of Pages: 300. Service: 03/13/2013 by

		email.. Pursuant to ECF-10, filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 03/19/2013. [58714]
03/21/13	103	NOTICE OF CALENDARING issued. Panel: 1305C. Calendar date/location: Tuesday, 05/07/2013 Washington, D.C. Courtroom 201. Response to oral argument order due: 04/15/2013 [60553]
05/07/13	114	Submitted after ORAL ARGUMENT by Evan Chesler for Mylan Pharmaceuticals Inc., Mylan Inc. and Natco Pharma Ltd., Ms. Deanne Maynard for Sandoz, Inc. and Momenta Pharmaceuticals Inc. and Elizabeth J. Holland for Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co., Ltd. and Teva Neuroscience, Inc.. Panel: Rader, Moore and Benson. [75097]
07/26/13	115	OPINION and JUDGMENT filed. The judgment or decision is: Affirmed-in-Part, Reversed-in-Part and Remanded. (Precedential Opinion). (For the Court: Rader,Chief Judge; Moore,Circuit

		Judge and Benson,United States District Judge). [94366]
09/16/13	119	Corrected Petition for panel rehearing, for en banc rehearing filed by Appellees Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc. and Yeda Research and Development Co., Ltd.. Service: 09/16/2013 by email. [103958]--[Edited 09/17/2013 by AT to add "corrected" to docket text]
10/18/13	121	ORDER filed denying [119] petition for panel rehearing filed by Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co., Ltd. and Teva Neuroscience, Inc.; denying [119] petition for en banc rehearing filed by Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co., Ltd. and Teva Neuroscience, Inc. The mandate will issue on 10/25/2013. By: En Banc (Per Curiam). Service: 10/18/2013 by clerk. [111261]
10/24/13	122	MOTION of Appellees Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc. and

		Yeda Research and Development Co., Ltd. to clarify [115] Opinion and Judgment filed 7/26/2013. Response/Opposition is due 11/07/2013 [Consent: opposed]. Service: 10/24/2013 by email. [112760]
10/24/13	123	MOTION of Appellees Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc. and Yeda Research and Development Co., Ltd. to stay execution of the mandate until pending filing of the Petition for Certiorari [Consent: opposed]. Service: 10/24/2013 by email. [112764]
11/01/13	124	ORDER filed denying [122] motion to clarify filed by Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co., Ltd. and Teva Neuroscience, Inc.; denying [123] motion to stay mandate filed by Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co., Ltd. and Teva Neuroscience, Inc.. By: Merits Panel (Per Curiam). Service: 11/01/2013 by clerk. [114260]

11/01/13	125	Mandate issued to the United States District Court for the Southern District of New York. Service: 11/01/2013 by clerk. [114268] [12-1567, 12-1568, 12-1569, 12-1570]
01/17/14	126	Petition for writ of Certiorari filed on 01/16/2014 in the Supreme Court of the United States. Supreme Court #: 12-1567, Inc. Teva Pharmaceuticals USA v. Inc. Sandoz.
04/23/14	128	The petition for writ of certiorari, [12-1567], filed on 01/16/2014, was Granted on 03/31/2014. [150118]

Relevant Docket Entries in U.S. District Court for the Southern District of New York, *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, Case No. 08-cv-7311

Date Filed	#	Docket Text
08/28/08	1	COMPLAINT against Sandoz, Inc., Sandoz International GmbH, Novartis AG, Momenta Pharmaceuticals, Inc.. (Filing Fee $ 350.00, Receipt Number 661755)Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. (Attachments: # 1 Exhibit)(jpo) (Entered: 09/02/2008)
11/03/08	16	ANSWER to Complaint with JURY DEMAND., COUNTERCLAIM against all plaintiffs. Document filed by Sandoz Inc..(Hagberg, Karen) (Entered: 11/03/2008)
12/08/08	20	ANSWER to Counterclaim. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc..(Lin, Hsin) (Entered: 12/08/2008)

12/08/08	21	ANSWER to Counterclaim. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc..(Lin, Hsin) (Entered: 12/08/2008)
09/22/09	67	JOINT CLAIM CONSTRUCTION STATEMENT. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc..(Jean, Patrice) (Entered: 09/22/2009)
10/07/09	68	SEALED DOCUMENT placed in vault.(nm) (Entered: 10/07/2009)
10/07/09	69	NOTICE of Materials Filed Under Seal re: Teva's Opening Brief on Claim Construction Issues. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 10/07/2009)
10/07/09	70	DECLARATION of Gregory A. Grant, Ph.D. in Support re: 68 Sealed Document. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda

		Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Attachments: # 1 Exhibit Exhibit A, # 2 Exhibit Exhibit B-1, # 3 Exhibit Exhibit B-2, # 4 Exhibit Exhibit B-3, # 5 Exhibit Exhibits C-F, # 6 Exhibit Exhibit G, # 7 Exhibit Exhibits H-L)(Jean, Patrice) (Entered: 10/07/2009)
10/07/09	71	CLAIM CONSTRUCTION STATEMENT. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Attachments: # 1 Affidavit Declaration of Frantisek Svec, Ph.D., # 2 Exhibit 1 to Svec Declaration, # 3 Exhibit 2 to Svec Declaration, # 4 Exhibit 3 to Svec Declaration, # 5Affidavit Declaration of Brian M. Kramer, # 6 Exhibit 1, part 1 to Kramer Declaration, # 7 Exhibit 1, part 2 to Kramer Declaration, # 8 Exhibit 2 to Kramer Declaration, # 9 Exhibit 3 to Kramer Declaration, # 10 Exhibit 4 to Kramer Declaration, # 11 Exhibit 5 to Kramer Declaration, # 12Exhibit 6 to Kramer Declaration, # 13 Exhibit 7 to Kramer Declaration, # 14 Exhibit 8 to Kramer Declaration, # 15 Exhibit 9 to Kramer Declaration, # 16 Exhibit 10 to Kramer Declaration, # 17 Exhibit 11 to Kramer Declaration, # 18 Exhibit 12

		to Kramer Declaration, # 19 Exhibit 13 to Kramer Declaration, # 20 Exhibit 14 to Kramer Declaration)(Doyle, David) (Entered: 10/07/2009)
10/08/09	72	DECLARATION of Gregory A Grant, Ph.D. in Support re: 70 Declaration in Support, 68 Sealed Document. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 10/08/2009)
11/04/09	76	NOTICE of Materials Filed Under Seal. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Blessing, Carolyn) (Entered: 11/04/2009)
11/04/09	77	DECLARATION of GREGORY A. GRANT, PH.D. in Support re: 76 Notice (Other). Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Attachments: # 1 Exhibit M to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., # 2 Exhibit N to

		SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., # 3 Exhibit O to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., # 4Exhibit P to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., # 5 Exhibit P1 to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., # 6 Exhibit P2 to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., # 7 Exhibit P3 to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., #8 Exhibit P4 to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., # 9 Exhibit P5 to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D., # 10 Exhibit P6 to SECOND SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D.)(Blessing, Carolyn) (Entered: 11/04/2009)
11/04/09	78	NOTICE of Materials Filed Under Seal. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Attachments: # 1 Proof of Service)(Doyle, David) (Entered:

11/04/2009)

11/04/09	79	DECLARATION of Robert C. Kohberger, Ph.D. re: 78 Notice (Other) *(Declaration In Support of Defendants Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s Opposition Claim Construction Brief)*. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Attachments: #1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10)(Doyle, David) (Entered: 11/04/2009)
11/04/09	80	DECLARATION of Jim Anderson, Ph.D. in Support re: 78 Notice (Other). Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Doyle, David) (Entered: 11/04/2009)
11/04/09	81	SEALED DOCUMENT placed in vault.(nm) (Entered: 11/05/2009)
11/04/09	82	SEALED DOCUMENT placed in vault.(jri) (Entered: 11/05/2009)
11/18/09	89	SEALED DOCUMENT placed in vault.(nm) (Entered: 11/18/2009)
11/18/09	90	SEALED DOCUMENT placed in vault.(jri) (Entered: 11/18/2009)
11/18/09	91	NOTICE of Materials Filed Under Seal re: Teva's Reply Brief on Claim

		Construction Issues. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 11/18/2009)
11/18/09	92	DECLARATION of Gregory A. Grant in Support re: 91 Notice (Other), Notice (Other). Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Attachments: # 1 Exhibit Exhibit Q to Third Supplemental Declaration of Gregory A. Grant, # 2 Exhibit Exhibit R to Third Supplemental Declaration of Gregory A. Grant)(Jean, Patrice) (Entered: 11/18/2009)
11/18/09	93	DECLARATION of Judith D. Goldberg in Support re: 91 Notice (Other), Notice (Other). Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Attachments: # 1 Exhibit Exhibit A to Declaration of Judith D. Goldberg)(Jean, Patrice) (Entered: 11/18/2009)

11/18/09	96	NOTICE of Materials Filed Under Seal In Support of Defendants Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s Reply Claim Construction Brief. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Doyle, David) (Entered: 11/18/2009)
11/25/09	97	SEALED DOCUMENT placed in vault.(nm) (Entered: 11/25/2009)
11/25/09	98	NOTICE of Materials Filed Under Seal re: Proposed Order Granting Teva's Motion for Leave to File a Sur-Reply Brief on Claim Construction Issues. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 11/25/2009)
11/25/09	99	MOTION for Leave to File Sur-Reply Brief on Claim Construction Issues and Accompanying Declaration. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc..(Jean, Patrice) (Entered: 11/25/2009)
11/25/09	100	MEMORANDUM OF LAW in Support re: 99 MOTION for Leave to

		File Sur-Reply Brief on Claim Construction Issues and Accompanying Declaration.. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 11/25/2009)
11/30/09	102	MEMO ENDORSED ON NOTICE OF PLAINTIFFS' MOTION FOR LEAVE TO FILE A SUR-REPLY ON CLAIM CONSTRUCTION ISSUES AND ACCOMPANYING DECLARATION OF CAROLYN A. BLESSING: ENDORSEMENT: Motion (Dkt. No. 99) is Granted. So Ordered. (Signed by Judge Andrew J. Peck on 11/30/09) (js) (Entered: 11/30/2009)
11/30/09	104	ENDORSED REPLY MEMORANDUM OF LAW re: 99 MOTION for Leave to File Sur-Reply Brief on Claim Construction Issues and Accompanying Declaration., 102 Memo Endorsement, *Teva's Sur-Reply Brief on Claim Construction Issues (Redacted Public Version).* Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda

		Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 11/30/2009)
11/30/09	105	DECLARATION of Carolyn A. Blessing (Redacted Public Version) in Support re: 104 Reply Memorandum of Law,. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 11/30/2009)
12/11/09	114	SEALED DOCUMENT placed in vault.(nm) (Entered: 12/11/2009)
12/11/09	115	MOTION for Leave to File Sur-Sur-Reply Brief on Claim Construction Issues. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc..(Aannestad, Anders) (Entered: 12/11/2009)
12/11/09	116	MEMORANDUM OF LAW in Support re: 115 MOTION for Leave to File Sur-Sur-Reply Brief on Claim Construction Issues.. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 12/11/2009)
12/11/09	117	NOTICE of Materials Filed Under Seal re: Proposed Order Granting Defendants Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s

		Motion for Leave to File a Sur-Sur-Reply Brief on Claim Construction Issues. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 12/11/2009)
12/14/09	118	ORDER GRANTING SANDOZ INC.'S AND MOMENTA PHARMACEUTICALS, INC.'S MOTION FOR LEAVE TO FILE A SUR-SUR-REPLY BRIEF ON CLAIM CONSTRUCTION ISSUES: It is hereby ordered that Sandoz, Inc.'s and Momenta Pharmaceuticals, Inc.'s motion be granted. Defendants are granted leave to file the sur-sur-reply brief on claim construction issues and accompanying declaration of Anders T. Aannestad. (Signed by Magistrate Judge Andrew J. Peck on 12/14/2009) Copies Faxed By Chambers.(jpo) (Entered: 12/14/2009)
12/23/09	120	SEALED DOCUMENT placed in vault.(nm) (Entered: 12/23/2009)
12/23/09	121	MOTION for Summary Judgment *of Invalidity for Indefiniteness Under 35 U.S.C. Section 112.* Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc..(Doyle, David) (Entered: 12/23/2009)

12/23/09	122	NOTICE of Materials Filed Under Seal In Support of Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s Motion for Summary Judgment of Invalidity for Indefiniteness Under 35 U.S.C. Section 112 re: 121 MOTION for Summary Judgment *of Invalidity for Indefiniteness Under 35 U.S.C. Section 112.*. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Doyle, David) (Entered: 12/23/2009)
01/22/10	126	NOTICE of Materials Filed Under Seal (Opposition to Defendants' Motion for Summary Judgment (Indefiniteness)) re: 121 MOTION for Summary Judgment *of Invalidity for Indefiniteness Under 35 U.S.C. Section 112.*. Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 01/22/2010)
01/22/10	127	DECLARATION of P Dubin in Support re: 126 Notice (Other), Notice (Other). Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Attachments: # 1 Exhibit Exhibit A

		(Declaration of P. Dubin in Support of Opposition to Defendants' Summary Judgment Motion (Indefiniteness)), # 2 Exhibit Exhibit B (Declaration of P. Dubin in Support of Opposition to Defendants' Summary Judgment Motion (Indefiniteness)), # 3 Exhibit Exhibit C (Declaration of P Dubin in Support of Opposition to Defendants' Summary Judgment Motion (Indefiniteness)))(Jean, Patrice) (Entered: 01/22/2010)
01/22/10	128	SEALED DOCUMENT placed in vault.(nm) (Entered: 01/25/2010)
02/01/10	133	TRANSCRIPT of proceedings held on January 20, 2010 9:30 a.m. before Judge Barbara S. Jones. (ajc) (Entered: 02/01/2010)
02/10/10	141	REPLY MEMORANDUM OF LAW in Support re: 121 MOTION for Summary Judgment *of Invalidity for Indefiniteness Under 35 U.S.C. Section 112. (Redacted Public Version).* Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 02/10/2010)
02/10/10	142	REPLY AFFIDAVIT of Brian M. Kramer in Support re: 121 MOTION for Summary Judgment *of Invalidity for Indefiniteness Under 35 U.S.C.*

Section 112.. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4Exhibit 4)(Aannestad, Anders) (Entered: 02/10/2010)

02/10/10 143 RESPONSE in Support re: 121 MOTION for Summary Judgment *of Invalidity for Indefiniteness Under 35 U.S.C. Section 112. Response to Plaintiffs' Statement of Material Facts.* Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 02/10/2010)

02/11/10 145 MEMORANDUM OF LAW in Support re: 144 MOTION to Strike Document No. 127 *Defendants Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s Objections to Evidence and Notice of Motion to Strike the Expert Declarations of Dr. Gregory Grant and Dr. Paul Dubin from Plaintiffs' O MOTION to Strike Document No. 127 Defendants Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s Objections to Evidence and Notice of Motion to Strike the Expert Declarations of Dr. Gregory Grant and Dr. Paul Dubin from Plaintiffs' O (Redacted Public*

Version). Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 02/11/2010)

02/11/10 146 DECLARATION of Karen L. Hagberg in Support re: 144 MOTION to Strike Document No. 127 *Defendants Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s Objections to Evidence and Notice of Motion to Strike the Expert Declarations of Dr. Gregory Grant and Dr. Paul Dubin from Plaintiffs' O MOTION to Strike Document No. 127 Defendants Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s Objections to Evidence and Notice of Motion to Strike the Expert Declarations of Dr. Gregory Grant and Dr. Paul Dubin from Plaintiffs' O. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2A, # 3 Exhibit 2B, # 4 Exhibit 3, # 5 Exhibit 4, # 6 Exhibit 5, # 7 Exhibit 6, # 8 Exhibit 7, # 9 Exhibit 8, # 10 Exhibit 9, # 11 Exhibit 10, # 12 Exhibit 11, # 13 Exhibit 12, #14 Exhibit 13, # 15 Exhibit 14, # 16 Exhibit 15, # 17 Exhibit 16, # 18 Exhibit 17, # 19 Exhibit 18, # 20 Exhibit 19, # 21 Exhibit 20, # 22Exhibit 21,*

 # 23 Exhibit 22, # 24 Exhibit 23, # 25 Exhibit 24)(Aannestad, Anders) (Entered: 02/11/2010)

02/11/10 147 NOTICE of Filing Materials Under Seal In Support of Defendants' Reply Brief In Support of Motion for Summary Judgment of Indefiniteness and Defendants' Objections to Evidence and Motion to Strike Expert Declarations from Plaintiffs' Opposition to Motion for Summary Judgment of Indefiniteness. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 02/11/2010)

02/11/10 148 SEALED DOCUMENT placed in vault.(nm) (Entered: 02/16/2010)

02/25/10 149 MOTION to Strike. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc.. (Attachments: # 1 Text of Proposed Order, # 2 Text of Proposed Order)(Hashmall, David) (Entered: 02/25/2010)

02/25/10 150 NOTICE of MATERIALS FILED UNDER SEAL re: 149 MOTION to Strike.. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.,

		Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc.. (Hashmall, David) (Entered: 02/25/2010)
02/25/10	151	SEALED DOCUMENT placed in vault.(nm) (Entered: 03/01/2010)
03/08/10	155	NOTICE of Materials Filed Under Seal (Opposition to Motion to Strike Expert Declarations of Dubin and Grant). Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 03/08/2010)
03/08/10	156	SEALED DOCUMENT placed in vault.(nm) (Entered: 03/09/2010)
03/15/10	157	NOTICE of of Materials Filed Under Seal in Support of Defendants' Motion for Leave to File First Amended Answer and in Opposition to Plaintiffs' Cross-Motion to Strike. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 03/15/2010)
03/15/10	158	SEALED DOCUMENT placed in vault.(nm) (Entered: 03/16/2010)
03/18/10	159	SEALED DOCUMENT placed in vault.(jri) (Entered: 03/18/2010)

03/18/10	160	NOTICE of of Reply Brief Filed Under Seal in Support of Defendants Sandoz Inc.'s and Momenta Pharmaceuticals, Inc.'s Objections to Evidence and Motion to Strike Expert Declarations From Plaintiffs' Opposition to Motion for Summary Judgment of Indefiniteness. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Kramer, Brian) (Entered: 03/18/2010)
03/25/10	162	SEALED DOCUMENT placed in vault.(nm) (Entered: 03/25/2010)
03/25/10	163	NOTICE of Materials Filed Under Seal (Reply Brief ISO Plaintiffs' Cross Motion to Strike Defendants' Expert Reports and Supporting Crystal Declaration). Document filed by Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc.. (Jean, Patrice) (Entered: 03/25/2010)
08/26/10	180	STIPULATION AND ORDER OF DISMISSAL: It is hereby ordered adjudged and decreed that all claims and asserted against Novartis AG and Sandoz International GmbH in Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc., 08cv7611 (BSJ) are hereby dismissed without prejudice. It is further ordered that all costs,

		expenses and attorneys' fees are to be borne by the party that incurred them. (Signed by Judge Barbara S. Jones on 8/26/2010) (jpo) (Entered: 08/26/2010)
09/07/10	181	MEMORANDUM AND ORDER, that Defendants' motions for summary judgment (Dkt. 121) and to strike the expert declarations of Dr. Grant and Dr. Dubin (Dkt. 144) are DENIED. (Signed by Judge Barbara S. Jones on 9/7/10) (pl) (Entered: 09/07/2010)
09/30/10	192	SEALED DOCUMENT placed in vault.(nm) (Entered: 09/30/2010)
09/30/10	193	SEALED DOCUMENT placed in vault.(nm) (Entered: 09/30/2010)
09/30/10	194	AMENDED ANSWER to 1 Complaint,., COUNTERCLAIM against Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. Document filed by Sandoz Inc.. (Doyle, David) (Entered: 09/30/2010)
09/30/10	195	AMENDED ANSWER to 1 Complaint,., COUNTERCLAIM against Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and

		Development Co. Ltd.. Document filed by Momenta Pharmaceuticals, Inc.. (Doyle, David) (Entered: 09/30/2010)
10/12/10	197	ORDER: For the reasons provided above, Plaintiffs' request for an order directing Defendants to provide the Court and Plaintiffs with ten days notice prior to launch of Defendants' intent and ability to launch their product is DENIED. (Signed by Judge Barbara S. Jones on 10/12/2010) (jpo) (Entered: 10/12/2010)
10/22/10	201	ANSWER to Counterclaim. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd..(Hashmall, David) (Entered: 10/22/2010)
10/22/10	202	ANSWER to Counterclaim. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd..(Hashmall, David) (Entered: 10/22/2010)
10/29/10	203	ORDER, further to the Court's Order dated October 22, 2010 (Case

		No. 08-7611, D.I. 200), the above-captioned cases are hereby consolidated. At the October 22, 2010 status conference, the following deadlines were agreed to by the parties: Plaintiffs will file an opposition to Defendants' Supplemental Claim Construction Brief no later than November 22, 2010; Defendants will file a reply to Plaintiffs' Opposition to Defendants' Supplemental Claim Construction Brief no later than December 3, 2010. (Responses due by 11/22/2010, Replies due by 12/3/2010) (Signed by Judge Barbara S. Jones on 10/28/2010) (lnl) (Entered: 10/29/2010)
11/22/10	204	NOTICE of Materials Filed Under Seal (Plaintiffs' Opposition to Defendants' Supplemental Claim Construction Brief). Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Jean, Patrice) (Entered: 11/22/2010)
11/22/10	205	SEALED DOCUMENT placed in vault.(nm) (Entered: 11/23/2010)
12/03/10	206	BRIEF *in REPLY, in Support of Supplemental Claim Construction Brief*. Document filed by Momenta

		Pharmaceuticals, Inc., Sandoz Inc.. (Attachments: # 1 Declaration of Karen Hagberg)Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ-AJP(Doyle, David) (Entered: 12/03/2010)
12/03/10	208	SEALED DOCUMENT placed in vault.(cb) (Entered: 12/06/2010)
12/06/10	207	NOTICE of Materials Filed Under Seal. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ-AJP(Doyle, David) (Entered: 12/06/2010)
02/09/11	213	TRANSCRIPT of proceedings held on 1/19/11 before Judge Barbara S. Jones. (jw) (Entered: 02/09/2011)
08/22/11	271	JOINT PRETRIAL STATEMENT. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc., Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Attachments: # 1 Exhibit A, # 2Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F)(Hashmall, David) (Entered: 08/22/2011)
08/26/11	272	NOTICE of Statement of Claims and Defenses re: (264 in 1:08-cv-07611-

		BSJ -AJP) Order,. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Aannestad, Anders) (Entered: 08/26/2011)
08/29/11	273	MEMORANDUM AND ORDER, the disputed claim terms shall have the constructions set forth in this Order. In view of the Court's finding that the claims are capable of construction, Mylan's motion for a summary judgment finding of invalidity on the basis of indefiniteness (Dkt. 96 in 09 Ci v. 8824 (BSJ) (AJP)) is DENIED. The Clerk of the Court is directed to terminate this motion. in case 1:08-cv-07611-BSJ -AJP; denying (96) Motion for Summary Judgment in case 1:09-cv-08824-BSJ. (Signed by Judge Barbara S. Jones on 8/24/11) Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(pl) (Entered: 08/29/2011)
08/30/11	274	SEALED DOCUMENT placed in vault.(nm) (Entered: 08/30/2011)
08/30/11	275	SEALED DOCUMENT placed in vault.(nm) (Entered: 08/30/2011)
08/30/11	276	NOTICE of Filing Plaintiffs' Pre-trial Brief Under Seal. Document filed by Teva Neuroscience, Inc.,

		Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Jean, Patrice) (Entered: 08/30/2011)
08/30/11	277	PRETRIAL STATEMENT *Plaintiffs' Statement of the Elements of Each Claim or Defense*. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd..(Jean, Patrice) (Entered: 08/30/2011)
09/06/11	278	TRANSCRIPT of Proceedings re: Conference held on 8/30/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Guido Tascione, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 9/30/2011. Redacted Transcript Deadline set for 10/10/2011. Release of Transcript Restriction set for 12/8/2011.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 09/06/2011)

09/12/11	280	JOINT STIPULATION AND ORDER REGARDING "PHARMACEUTICAL COMPOSITION COMPRISING" AND "PHARMACEUTICALLY ACCEPTABLE EXCIPIENT" LIMITATIONS IN CLAIMS 12, 23, 30, AND 31 OF U.S. PATENT NO. 6,939,539: It is hereby Stipulated and Agreed by and between the parties, through their undersigned counsel that: Sandoz stipulates for purposes of this case that ANDA No. 90-218 literally meets the "pharmaceutical composition comprising" and "pharmaceutically accecptable excipient" limitations of Claim 12, 23, 30 and 31 of U.S. Patent No. 6,939,539.Teva will not call Dr. Paul Jarosz as a witness at trial. Teva will continue to have the burden of proof regarding all other claim limitations in Claim 12, 23, 30 and 31 of U.S. Patent No. 6,939,539; and Sandoz will have the right to argue that it does not meet the remaining claim limitations in Claims 12, 23, 30 and 31. (Signed by Judge Barbara S. Jones on 9/9/2011) (mro) (Entered: 09/12/2011)
09/12/11	281	TRANSCRIPT of Proceedings re: Conference held on 8/30/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Guido

		Tascione, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/6/2011. Redacted Transcript Deadline set for 10/17/2011. Release of Transcript Restriction set for 12/15/2011.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 09/12/2011)
10/04/11	284	TRANSCRIPT of Proceedings re: Trial held on 9/7/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012. (Attachments: # 1 transcript)Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered:

10/04/2011)

10/04/11	286	TRANSCRIPT of Proceedings re: Trial held on 9/8/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	288	TRANSCRIPT of Proceedings re: Trial held on 9/9/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for

		11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	290	TRANSCRIPT of Proceedings re: TRIAL held on 9/13/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	292	TRANSCRIPT of Proceedings re: TRIAL held on 9/14/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript

		Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	294	TRANSCRIPT of Proceedings re: Trial held on 9/15/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	296	TRANSCRIPT of Proceedings re: TRIAL held on 9/16/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be

		viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	298	TRANSCRIPT of Proceedings re: Trial held on 9/19/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012. (Attachments: # 1 transcript)Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)

10/04/11	300	TRANSCRIPT of Proceedings re: TRIAL held on 9/20/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	302	TRANSCRIPT of Proceedings re: Trial held on 9/21/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases:

		1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/11/11	304	NOTICE of Materials Filed Under Seal. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Hashmall, David) (Entered: 10/11/2011)
10/11/11	305	NOTICE of of Materials Filed Under Seal. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 10/11/2011)
10/11/11	306	SEALED DOCUMENT placed in vault.(mps) (Entered: 10/12/2011)
10/11/11	307	SEALED DOCUMENT placed in vault.(nm) (Entered: 10/12/2011)
10/24/11	308	NOTICE of Materials Filed Under Seal. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Ebie, Kenneth) (Entered: 10/24/2011)
10/24/11	309	NOTICE of Materials Filed Under Seal. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd.,

		Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Blessing, Carolyn) (Entered: 10/24/2011)
10/24/11	310	POST TRIAL MEMORANDUM. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd..(Blessing, Carolyn) (Entered: 10/24/2011)
10/24/11	311	DECLARATION of C. Blessing in Support re: 310 Post Trial Memorandum. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Attachments: # 1 Exhibit Exhibit A)(Blessing, Carolyn) (Entered: 10/24/2011)
10/24/11	312	SEALED DOCUMENT placed in vault.(nm) (Entered: 10/25/2011)
10/24/11	313	SEALED DOCUMENT placed in vault.(mps) Modified on 10/25/2011 (mps). (Entered: 10/25/2011)
10/25/11	314	NOTICE of Materials Filed Under Seal. Document filed by Sandoz Inc.. (Aannestad, Anders) (Entered: 10/25/2011)

10/26/11	316	PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd..(Hashmall, David) (Entered: 10/26/2011)
10/31/11	317	NOTICE of Materials Filed Under Seal. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Blessing, Carolyn) (Entered: 10/31/2011)
10/31/11	318	SEALED DOCUMENT placed in vault.(mps) (Entered: 11/01/2011)
10/31/11	319	SEALED DOCUMENT placed in vault.(nm) (Entered: 11/01/2011)
11/01/11	320	NOTICE of Materials Filed Under Seal. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Aannestad, Anders) (Entered: 11/01/2011)
11/01/11	321	NOTICE of Materials Filed Under Seal. Document filed by Mylan Inc.,

		Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Ebie, Kenneth) (Entered: 11/01/2011)
11/14/11	322	RESPONSE *to Plaintiffs' Proposed Findings of Fact and Conclusions of Law (redacted).* Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Solano, Ricardo) (Entered: 11/14/2011)
11/14/11	323	REPLY *in Support of Post-Trial Findings of Facts and Conclusions of Law.* Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Solano, Ricardo) (Entered: 11/14/2011)
11/15/11	324	PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc..Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Doyle, David) (Entered: 11/15/2011)
11/15/11	325	RESPONSE *to Plaintiffs' Proposed Findings of Fact and Conclusions of Law (redacted).* Document filed by

		Momenta Pharmaceuticals, Inc., Sandoz, Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Doyle, David) (Entered: 11/15/2011)
11/15/11	326	REPLY *to Plaintiffs' Opposition to Sandoz, Inc. and Momenta Pharmaceuticals, Inc.'s Proposed Findings of Fact and Conclusions of Law (redacted).* Document filed by Momenta Pharmaceuticals, Inc., Sandoz, Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Doyle, David) (Entered: 11/15/2011)
11/16/11	327	RESPONSE *in Opposition to Defendants' Proposed Findings of Fact and Conclusions of Law (Redacted).* Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Hashmall, David) (Entered: 11/16/2011)
11/16/11	328	REPLY *to Defendants' Proposed Findings of Fact and Conclusions of Law (Redacted).* Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Hashmall, David) (Entered:

11/16/2011)

01/05/12	329	TRANSCRIPT of Proceedings re: Conference held on 11/3/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Tara Jones, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 1/30/2012. Redacted Transcript Deadline set for 2/9/2012. Release of Transcript Restriction set for 4/9/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 01/05/2012)
06/22/12	334	ORDER: After a bench trial and the Court's review of the parties' post-trial briefing, the Court finds that the Defendants', Mylan Pharmaceuticals Inc., et al. and Sandoz, Inc. et al., abbreviated new drug applications infringe all of the asserted claims of the Plaintiffs' patents and that none of the asserted claims are invalid or unenforceable. The full opinion of the Court's findings of fact and conclusions of law will follow immediately after the parties have

		had the opportunity to review it in order to request redactions of any proprietary information it may contain. See Dkt. No. 332 in 08-cv-7611.) (Signed by Judge Barbara S. Jones on 6/22/2012) Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(laq) (Entered: 06/22/2012)
06/29/12	335	SEALED DOCUMENT placed in vault.(mps) (Entered: 06/29/2012)
06/29/12	336	OPINION AND ORDER # 102065: For the reasons provided within, the Court finds that both Mylan's and Sandoz's ANDA infringe all of the asserted claims, and that none of the asserted claims are invalid or unenforceable. Teva is ordered to submit a proposed judgment incorporating the rulings contained in this Opinion and Order to the Court on or before July 2, 2012. (Signed by Judge Barbara S. Jones on 6/22/2012) Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(laq) Modified on 7/16/2012 (ft). (Entered: 06/29/2012)
07/24/12	338	FINAL JUDGMENT that 1. for the reasons set forth in the Court's Opinion dated June 22, 2012, that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE SANDOZ

DEFENDANTS with respect to Plaintiffs' claims that the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 nfringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10,12, 23, 30, and 31 ofthe '539 patent, claims 1 and 2 of the '430 patent, and claims 1 and 6 of the '847 patent pursuant to 35 U.S.C. § 271(e)(2)(A), and that each of these asserted claims against the Sandoz Defendants is valid, enforceable, and infringed;2. IT IS FURTHER ORDERED AND. ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE SANDOZ DEFENDANTS with respect to Plaintiffs' declaratory judgment claims pursuant to 35 U.S.C. §§ 2201,2202, that the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 if commercially manufactured, used, marketed, sold, or offered for sale within the United States or imported thereto would infringe claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1 and 2 of the '430 patent, claims 1 and 6 of the '847 patent against the Sandoz Defendants pursuant to 35 U.S.C. §§

271(a), (b), and (c), and IT IS DECLARED that each of these asserted clai.ms against the Sandoz Defendants is valid, enforceable, and infringed; 3. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE SANDOZ DEFENDANTS with respect to the Sandoz Defendants' counterclaims seeking declaratory judgment of non-infringement, invalidity and unenforccability of claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1 and 2 of the '430 patent, claims l and 6 of the '847 patent, claim 1 of the '589 patent, claim 1 ofthe '476 patent, claim 1 of the '161 patent, claim 1 of the '808 patent, and claims 1 and 2 of the '898 patent, all such counterclaims are DISMISSED WITH PREJUDICE, and IT IS DECLARED that each of these asserted claims against the Sandoz Defendants is valid, enforceable, and infringed by the product which is the subject of the Sandoz Defendants' ANDA No. 90-218; 4. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT ISENTERED IN FAVOR OF PLAINTIFFS and

AGAINST THE MYLAN DEFENDANTS with respect to Plaintiffs' claims that the product which is the subject of the Mylan Defendants' ANDA No. 91-646 infringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23. 30, and 31 of the '539 patent, claims 1, 2, and 3 of the '430 patent, claims 1 and 6 of the '847 patent, claim l of the '589 patent, claim 1 ofthe '476 patent, and claim 1 of the '161 patent pursuant to 35U.S.C. §271 (e)(2)(A), and that each of these asserted claims against the MylanDefendants is valid, enforceable, and infringed; 5. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE MYLAN DEFENDANTS with respect to Plaintiffs' declaratory judgment claims pursuant to pursuant to 35 U.S.C. §§ 2201, 2202, that the product which is the subject of the My1an Defendants' ANDA No. 91-646 if commercially manufactured, used, marketed, sold, or offered for sale within the United States or imported thereto would infringe claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31

of the '539 patent, claims l, 2, and 3 of the '430 patent, claim l of the '589 patent, claim 1 of the '476 patent, claim 1 of the' 161 patent, claims 1 and 6 of the '847 patent against the Mylan Defendants pursuant to 35 U.S.C. §§ 27l(a), (b), (c), and IT IS DECLARED that each of these asserted claims against the Mylan Defendants is valid, enforceable, and infringed; 6. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT ISENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE MYLAN DEFENDANTS with respect to the My1an Defendants' counterclaims seeking declaratory judgment of non-infringement invalidity, and unenforceability of claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1, 2, and 3 of the '430 patent, claim 1 of the '589 patent, claim 1 of the '4 7 6 patent, claim 1 of the '161 patent, claim 1 of the '808 patent, claims 1and 6 of the '847 patent, and claims 1, 2, and 3 of the '898 patent, all suchcounterclaims are DISMISSED WIT1l PREJUDICE, and IT IS DECLARED that each of these asserted claimsagainst the Mylan Defendants is valid, enforceable,and infringed by the

product which is the subject of the Mylan Defendants'ANDA No. 91-646; 7. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 27l(e)(4)(A), the effective date of any approval by the U.S. Food and Drug Administration ("FDA") of the Sandoz Defendants' ANDA No. 9Q-218 shall not be earlier than the expiration ofthe '098 patent, the '539 patent, the '589 patent, the '476 patent, the '161 patent, the '430 patent, and the '847 patent on May 24,2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable, the date any such exclusivity ends, but that Plaintiffs will provide written notice to the Sandoz Defendants of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA; 8. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271 (e)(4)(A), the effective date of any approval by the FDA of the Mylan Defendants' ANDA No. 91-646 shall not be earlier than the expiration of the '098 patent, the '539 patent, the '589 patent, the '476 patent, the '161 patent, the '430 patent, and the '847 patent on May 24,2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable,

the date any such exclusivity ends, but that Plaintiffs will provide written notice to the Mylan Defendants of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA; 9. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 27l(eX4)(B), the Sandoz Defendants and each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of the Sandoz Defendants' ANDA No. 90~218, which infringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, claim 1 of the' 161 patent. claims 1 and 2 of the '430 patent, and claims 1 and 6 of the '847 patent until May 24, 2014; 10. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(B), the Mylan Defendants, each of their officers, agents, servants, employees and attorneys, and those persons in

active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of the Mylan Defendants' ANDA No. 91-646, which infringes claims 1 and 8 ofthe '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, clahn 1 of the '161 patent, claims 1, 2, and 3 ofthc '430 patent, and claims 1 and 6 of the '847 patent until May 24, 2014; 11. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 283, the Sandoz Defendants, their respective officers, directors, employees, agents, successors, affiliates and assigns, and all persons and entities acting in concert or participation with them are permanently enjoined from directly or indirectly engaging in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 until the expiration of the '808 patent on September 1, 2015,

and are permanently enjoined from directly or indirectly engaging in the commercialmanufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject ofthe Sandoz Defendants' ANDA No. 90-218 until the expiration of the '098 patent, the '539 patent, the '430 patent, the '589 patent, the '476 patent, the '161 patent, the '847 patent, and the patent '898 patent on May 24, 2014; 12. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 283, the MylanDefendants, their respective officers, directors, employees, agents, successors,affiliates and assigns, and all persons and entities acting in concert or participation with them are permanently enjoined from directly or indirectly engagjng in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Mylan Defendants' ANDA No. 91646 until the expiration of the '808 patent on September 1, 2015, and are permanently enjoined from directly or indirectly engaging in the commercial manufacture, use,

marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Mylan Defendants' ANDA No. 91-646 until the expiration of the '098 patent, the '539 patent, the '430 patent, the '589 patent, the '476 patent, the '161 patent, the '847 patent, and the patent '898 patent on May 24, 2014; 13. IT IS FURTHER ORDERED THAT nothing in this FINAL JUDGMENT ORDER shall be construed to limit the rights of the parties pursuant to 35 U.S.C. § 27l(e)(l); 14. IT IS FURTHER ORDERED that the Sandoz Defendants and the Mylan Defendants do not waive any rights to appeal any portion of this final judgment including the injunctive relief granted, to the extent the Court's findings or holdings are modified on appeal; and 15. IT IS FURTHER ORDERED that any request for costs pursuant to Fed. R. Civ. P 54(d)(l) and Local Civil Rule 54.1 shall be filed within forty-five (45) days of entry of this FINAL JUDGMENT ORDER, and any motion for attorneys' fees pursuant to Fed. R. Civ. P. 54(d)(2) and 35 U.S.C. § 285 shall be filed within forty-five (45) days of entry of this

		FINAL JUDGMENT ORDER. The Sandoz Defendants' and the Mylan Defendants' opposition to any request for costs pursuant to Fed. R. Civ. P. S4(d)(l) and Local Civil Rule 54.1 shall be filed within ninety (90) days of the filing of such request, and the Sandoz Defendants' and the Mylan Defendants' opposition to any motion for attorneys' fees pursuant to Fed. R. Ciy. P 54(d)(2) and 35 U.S.C. § 285 shall be filed within ninety (90) days of the filing of such motion. Plaintiffs' reply in support of any motion for attorneys' fees shall be filed within thirty (30) days of the filing of opposition by the Sandoz or Mylan Defendants. (Signed by Judge Barbara S. Jones on 7/23/12) (Attachments: # 1 notice of right to appeal)(ml) Modified on 8/1/2012 (jar). (Entered: 07/24/2012)
07/26/12	339	NOTICE OF APPEAL TO THE FEDERAL CIRCUIT from (255 in 1:09-cv-08824-BSJ, 338 in 1:08-cv-07611-BSJ -AJP) Judgment,,,

		Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Doyle, David) (Entered: 07/26/2012)
07/26/12	340	NOTICE OF APPEAL TO THE FEDERAL CIRCUIT from (255 in 1:09-cv-08824-BSJ, 338 in 1:08-cv-07611-BSJ -AJP) Judgment. Form 7 and Form 22 are due within 14 days. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd. Filing fee $ 455.00, receipt number 465401044800. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ.(tp) (Entered: 07/27/2012)
08/08/12		USCA Case Number 12-1567 from the US Court of Appeals, Federal Circuit assigned to 339 Notice of Appeal to the Federal Circuit, filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (nd) (Entered: 08/08/2012)
08/08/12		USCA Case Number 12-1568 from the US Court of Appeals, Federal Circuit assigned to (340 in 1:08-cv-07611-BSJ -AJP, 257 in 1:09-cv-08824-BSJ) Notice of Appeal to the Federal Circuit, filed by Natco Pharma Ltd., Mylan Inc., Mylan Pharmaceuticals Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(nd)

(Entered: 08/08/2012)

07/26/13	344	OPINION of USCA for the Federal Circuit as to (340 in 1:08-cv-07611-BSJ-AJP, 257 in 1:09-cv-08824-BSJ) Notice of Appeal to the Federal Circuit, filed by Natco Pharma Ltd., Mylan Inc., Mylan Pharmaceuticals Inc., (256 in 1:09-cv-08824-BSJ, 339 in 1:08-cv-07611-BSJ-AJP) Notice of Appeal to the Federal Circuit, filed by Momenta Pharmaceuticals, Inc., Sandoz Inc. USCA Case Number 2012-1567, -1568, -1569, -1570. The defendants in these consolidated patent infringement actions (collectively, Appellants) appeal from the district court' judgment that various claims of the nine patents-in-suit asserted by the plaintiffs (collectively, Teva) are infringed, and from the court's holdings regarding indefiniteness, nonenablement, and obviousness. We hold that Group I claims are invalid for indefiniteness, but that Group II claims have not been proven indefinite. We also hold that the district court did not err in its conclusions that the claims are infringed, and that the Appellants failed to prove that the claims would have been obvious and are not enabled. Accordingly, we affirm the district court's judgments of

		infringement and no invalidity with respect to Group II claims, reverse its judgment of no invalidity with respect to Group I claims, and remand. Jan Horbaly, Clerk USCA for the Federal Circuit. Certified: 07/26/2013. Filed In Associated Cases: 1:08-cv-07611-BSJ-AJP, 1:09-cv-08824-BSJ(nd) (Entered: 07/26/2013)
11/01/13	345	MANDATE of USCA for the Federal Circuit (Certified Copy) as to (340 in 1:08-cv-07611-BSJ-AJP, 257 in 1:09-cv-08824-BSJ) Notice of Appeal to the Federal Circuit, filed by Natco Pharma Ltd., Mylan Inc., Mylan Pharmaceuticals Inc., (256 in 1:09-cv-08824-BSJ, 339 in 1:08-cv-07611-BSJ-AJP) Notice of Appeal to the Federal Circuit, filed by Momenta Pharmaceuticals, Inc., Sandoz Inc. USCA Case Number 12-1567; 12-1568; 12-1569; 12-1570. ln accordance with the judgment (344 Opinion) of this Court, entered July 26, 2013, and pursuant to Rule 41(a)of the Federal Rules of Appellate Procedure, the formal mandate is hereby issued. Jan Horbaly, Clerk USCA for the Federal Circuit. Issued As Mandate: 11/1/2013. (Attachments: # 1 Opinion)Filed In Associated Cases: 1:08-cv-07611-BSJ-AJP, 1:09-

		cv-08824-BSJ(nd) (Entered: 11/01/2013)
11/18/13		NOTICE OF CASE REASSIGNMENT to Judge William H. Pauley, III. Judge Barbara S. Jones is no longer assigned to the case. (pgu) (Entered: 11/18/2013)
12/16/13	352	CONSENT MOTION to Alter Judgment re: (255 in 1:09-cv-08824-WHP, 338 in 1:08-cv-07611-WHP-AJP) Judgment,,,

patent"), 6,362,161 ("the '161 patent"), and 6,054,430 ("the '430 patent") patent on May 24,2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable, the date any such exclusivity ends, but that Teva Pharmaceuticals USA, Inc., Teva Pharmaceuticals Industries Ltd., Teva Neuroscience, Inc. and Yeda Research and Development Co. Ltd (collectively, "Plaintiffs") will provide written notice to Sandoz of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA; 2. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval by the FDA of Mylan's ANDA No. 91-646 shall not be earlier than the expiration of the '098 patent, the '476 patent, the '161 patent, and the '430 patent on May 24, 2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable, the date any such exclusivity ends, but that Plaintiffs will provide written notice to Mylan of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA; 3. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 27l(e)(4)(B),

Sandoz and its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of Sandoz's ANDA No. 90-218, until the expiration of the '098 patent, the '476 patent, the '161 patent, and the '430 patent on May 24, 2014; 4. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 27l(e)(4)(B), Mylan and its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of Mylan's ANDA No. 91-646, until the expiration of the '098 patent, the '476 patent, the '161 patent, and the '430 patent on May 24, 2014; and 5. IT IS FURTHER ORDERED THAT nothing in this MODIFIED JUDGMENT shall be construed to limit the rights of the parties

pursuant to 35 U.S.C. § 271(e)(1).
(Signed by Judge William H. Pauley,
III on 12/20/13) (Attachments:
1 Notice of Right to Appeal)(ml)
(Entered: 12/23/2013)

Relevant Docket Entries in U.S. District Court for the Southern District of New York, *Teva Pharmaceuticals USA, Inc. v. Mylan Pharmaceuticals Inc.*, Case No. 09-cv-8824

Date Filed	#	Docket Text
10/16/09	1	COMPLAINT against Mylan Pharmaceuticals Inc., Mylan Inc., Natco Pharma Ltd. (Filing Fee $ 350.00, Receipt Number 702994)Document filed by Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc., Yeda Research and Development Co. Ltd. (Attachments: # 1 Exhibit)(mro) (Entered: 10/19/2009)
11/16/09	8	ANSWER to Complaint., COUNTERCLAIM against Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. Document filed by Mylan Pharmaceuticals Inc., Mylan Inc..(Jacob, Beth) (Entered: 11/16/2009)
12/07/09	19	ANSWER to Counterclaim. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva

		Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc..(Jean, Patrice) (Entered: 12/07/2009)
03/04/10	34	ANSWER to Complaint., COUNTERCLAIM against Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. Document filed by Natco Pharma Ltd..(Jacob, Beth) (Entered: 03/04/2010)
03/29/10	36	ANSWER to Counterclaim. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc..(Hashmall, David) (Entered: 03/29/2010)
04/02/10	37	JOINT CLAIM CONSTRUCTION STATEMENT. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc..(Jean, Patrice) (Entered: 04/02/2010)
04/20/10	39	DECLARATION of Gregory A. Grant, Ph.D.. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical

		Industries, Ltd., Teva Neuroscience, Inc.. (Attachments: # 1 Declaration of Gregory A. Grant, Ph.D. (Part II of II), # 2 Exhibit A, # 3 Exhibit B (Part I of II), # 4 Exhibit B (Part II of II), # 5 Exhibit C, #6 Exhibit D, # 7 Exhibit E, # 8 Exhibit F, # 9 Exhibit G, # 10 Exhibit H, # 11 Exhibit I, # 12 Exhibit J, # 13 Exhibit K, # 14Exhibit L, # 15 Exhibit M, # 16 Certificate of Service of Joseph B. Crystal)(Crystal, Joseph) (Entered: 04/20/2010)
04/20/10	41	SEALED DOCUMENT placed in vault.(nm) (Entered: 04/22/2010)
05/21/10	43	NOTICE of Materials Filed Under Seal. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. (Crystal, Joseph) (Entered: 05/21/2010)
05/21/10	44	DECLARATION of Paul L. Dubin, PH.D. *with Exhibits A-M1.* Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. (Attachments: # 1Exhibit A, # 2 Exhibit B, # 3 Exhibit C,

		# 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit E-2, # 7 Exhibit F, # 8 Exhibit G, # 9 Exhibit H, # 10 Exhibit I, # 11 Exhibit J, # 12 Exhibit K, # 13 Exhibit L, # 14 Exhibit M-1)(Crystal, Joseph) (Entered: 05/21/2010)
05/21/10	45	DECLARATION of Paul L. Dubin, PH.D. re: 44 Declaration, *with Exhibits M2-X*. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. (Attachments: # 1 Exhibit N, # 2 Exhibit O-1, # 3 Exhibit O-2, # 4 Exhibit O-3, # 5 Exhibit O-4, # 6 Exhibit O-5, # 7 Exhibit O-6, # 8 Exhibit O-7, # 9 Exhibit P, # 10 Exhibit Q, # 11 Exhibit R, # 12 Exhibit S, # 13 Exhibit T, # 14 Exhibit U, # 15Exhibit V, # 16 Exhibit W, # 17 Exhibit X)(Crystal, Joseph) (Entered: 05/21/2010)
05/25/10	49	SEALED DOCUMENT placed in vault.(nm) (Entered: 05/26/2010)
05/26/10	48	SEALED DOCUMENT placed in vault.(cb) (Entered: 05/26/2010)
06/09/10	52	SEALED DOCUMENT placed in vault.(nm) (Entered: 06/09/2010)

07/09/10	57	NOTICE of Materials Filed Under Seal. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. (Crystal, Joseph) (Entered: 07/09/2010)
07/09/10	58	REPLY *Brief on Claim Construction Issues (REDACTED VERSION).* Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. (Crystal, Joseph) (Entered: 07/09/2010)
07/09/10	59	DECLARATION of Joseph B. Crystal in Support of Teva's Reply Brief on Claim Construction Issues (REDACTED VERSION) re: 58 Reply. Document filed by Yeda Research and Development Co. Ltd., Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. (Attachments: # 1 Exhibit (Exhibits 38-44))(Crystal, Joseph) (Entered: 07/09/2010)
07/09/10	60	DECLARATION of Gregory A. Grant, PH.D (REDACTED VERSION) re: 58 Reply. Document filed by Yeda Research and Development Co. Ltd., Teva

		Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Teva Neuroscience, Inc.. (Attachments: # 1 Exhibit (Exhibits 21 24), # 2 Exhibit (Exhibits 25A 25C), # 3 Exhibit (Exhibits 25D 25G), # 4 Exhibit (Exhibit 26 30))(Crystal, Joseph) (Entered: 07/09/2010)
07/09/10	61	SEALED DOCUMENT placed in vault.(nm) (Entered: 07/12/2010)
07/09/10	62	SEALED DOCUMENT placed in vault.(nm) (Entered: 07/12/2010)
07/12/10	63	BRIEF *Defendants' Reply Claim Construction Brief*. Document filed by Mylan Pharmaceuticals Inc., Mylan Inc., Natco Pharma Ltd..(Jacob, Beth) (Entered: 07/12/2010)
07/12/10	64	DECLARATION of Chang Ryu, Ph.D re: 63 Brief *Third Declaration*. Document filed by Mylan Pharmaceuticals Inc., Mylan Inc., Natco Pharma Ltd.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, #7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9)(Jacob, Beth) (Entered: 07/12/2010)
07/12/10	65	DECLARATION of Brandon M. White in Support re: 63 Brief.

		Document filed by Mylan Pharmaceuticals Inc., Mylan Inc., Natco Pharma Ltd.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7Exhibit G, # 8 Exhibit H)(Jacob, Beth) (Entered: 07/12/2010)
10/29/10	90	ORDER, further to the Court's Order dated October 22, 2010 (Case No. 08-7611, D.I. 200), the above-captioned cases are hereby consolidated. At the October 22, 2010 status conference, the following deadlines were agreed to by the parties: Defendants will file a letter brief in support of a motion for summary judgment of indefiniteness no later than November 15, 2010; Defendants will serve Plaintiffs with a Proposed Amended Answer and Counterclaims no later than November 15, 2010; Plaintiffs will inform Defendants whether they intend to oppose the filing of Defendants' Proposed Amended Answer and Counterclaims no later than November 22, 2010. Should Plaintiffs oppose the filing of the proposed amended pleading, the parties will meet and confer regarding a schedule to brief the issue; Plaintiffs will file an opposition to Defendants' motion for

		summary judgment of indefiniteness no later than December 6, 2010; On January 12,2011 at 10 a.m., the Court will hear oral argument regarding the indefiniteness issues raised by Defendants' motion for summary judgment and proposed claim constructions. (Brief in support of motion for summary judgment of indefiniteness due by 11/15/2010. Oral Argument set for 1/12/2011 at 10:00 AM before Judge Barbara S. Jones. Opposition to Defendant's motion for summary judgment of indefiniteness due by 12/6/2010) (Signed by Judge Barbara S. Jones on 10/28/2010) (lnl) (Entered: 10/29/2010)
12/03/10	92	BRIEF *in REPLY, in Support of Supplemental Claim Construction Brief*. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (Attachments: # 1 Declaration of Karen Hagberg)Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ-AJP(Doyle, David) (Entered: 12/03/2010)
12/06/10	93	NOTICE of Materials Filed Under Seal. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ-AJP(Doyle, David) (Entered:

12/06/2010)

12/06/10	94	NOTICE of Materials Filed Under Seal (Letter Brief in Opposition to Defendants' Motion for Summary Judgment and Supporting Blessing Declaration and Exhibits). Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Blessing, Carolyn) (Entered: 12/06/2010)
12/06/10	95	SEALED DOCUMENT placed in vault.(cb) (Entered: 12/07/2010)
12/17/10	96	MOTION for Summary Judgment *(redacted version of 11/15/10 letter to Court pursuant to the Protective Order (D.I. 54)).* Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd..(Solano, Ricardo) (Entered: 12/17/2010)
12/17/10	97	RESPONSE in Opposition re: 96 MOTION for Summary Judgment *(redacted version of 11/15/10 letter to Court pursuant to the Protective Order (D.I. 54)). (Redacted Public Version).* Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd.,

		Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Blessing, Carolyn) (Entered: 12/17/2010)
12/17/10	98	DECLARATION of Carolyn A. Blessing (Redacted Public Version) in Support re: 97 Response in Opposition to Motion, 94Notice (Other), Notice (Other). Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Attachments: # 1 Exhibit A to Blessing Dec ISO Letter Brief IOT Defendants' MSJ (Redacted Public Version), # 2 Exhibit B to Blessing Dec ISO Letter Brief IOT Defendants' MSJ (Redacted Public Version), # 3 Exhibit C to Blessing Dec ISO Letter Brief IOT Defendants' MSJ (Redacted Public Version), # 4 Exhibit D to Blessing Dec ISO Letter Brief IOT Defendants' MSJ (Redacted Public Version), # 5 Exhibit E to Blessing Dec ISO Letter Brief IOT Defendants' MSJ (Redacted Public Version))(Blessing, Carolyn) (Entered: 12/17/2010)
01/11/11	105	SEALED DOCUMENT placed in vault.(cb) Modified on 1/13/2011 (cb).

(Entered: 01/13/2011)

01/18/11	107	NOTICE of Materials Filed Under Seal (Plaintiffs' Answer to Mylan's First Amended Counterclaims and Plaintiffs' Answer to Natco's First Amended Counterclaims). Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Crystal, Joseph) (Entered: 01/18/2011)
01/18/11	108	SEALED DOCUMENT placed in vault.(cb) (Entered: 01/19/2011)
01/21/11	109	REPLY MEMORANDUM OF LAW in Support re: 96 MOTION for Summary Judgment *(redacted version of 11/15/10 letter to Court pursuant to the Protective Order (D.I. 54))*.. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. (Solano, Ricardo) (Entered: 01/21/2011)
02/09/11		TRANSCRIPT of proceedings held on 1/19/11 before Judge Barbara S. Jones. Refer to 08 cv 7611. (jw) (Entered: 02/09/2011)
08/22/11	192	JOINT PRETRIAL STATEMENT. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd., Teva Neuroscience, Inc., Teva Pharmaceutical

		Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F)(Hashmall, David) (Entered: 08/22/2011)
08/26/11	193	NOTICE of Statement of Claims and Defenses re: (264 in 1:08-cv-07611-BSJ -AJP) Order,. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Aannestad, Anders) (Entered: 08/26/2011)
08/29/11	194	MEMORANDUM AND ORDER, the disputed claim terms shall have the constructions set forth in this Order. In view of the Court's finding that the claims are capable of construction, Mylan's motion for a summary judgment finding of invalidity on the basis of indefiniteness (Dkt. 96 in 09 Ci v. 8824 (BSJ) (AJP)) is DENIED. The Clerk of the Court is directed to terminate this motion. in case 1:08-cv-07611-BSJ -AJP; denying (96) Motion for Summary Judgment in case 1:09-cv-08824-BSJ. (Signed by Judge Barbara S. Jones on 8/24/11) Filed In Associated Cases: 1:08-cv-

07611-BSJ -AJP, 1:09-cv-08824-BSJ(pl) (Entered: 08/29/2011)

08/30/11 195 PRETRIAL STATEMENT *Mylan's Statement of Elements of Claims.* Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd..(Solano, Ricardo) (Entered: 08/30/2011)

08/30/11 196 NOTICE of Materials Filed Under Seal. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. (Ebie, Kenneth) (Entered: 08/30/2011)

08/30/11 197 SEALED DOCUMENT placed in vault.(nm) (Entered: 08/30/2011)

09/06/11 198 TRANSCRIPT of Proceedings re: Conference held on 8/30/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Guido Tascione, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 9/30/2011. Redacted Transcript Deadline set for 10/10/2011. Release of Transcript Restriction set for 12/8/2011.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-

		08824-BSJ(McGuirk, Kelly) (Entered: 09/06/2011)
09/12/11	201	STIPULATION AND ORDER REGARDING "PHARMACEUTICAL COMPOSITION" AND "PHARMACEUTICALLY ACCEPTABLE EXCIPIENT" LIMITATIONS IN CLAIMS 12, 23, 30, AND 31 OF U.S. PATENT NO. 6,939,539: It is hereby Stipulated and Agreed by and between the parties, through their undersigned counsel that: Mylan's proposed glatiramer acetate product, pursuant to ANDA No. 91-646, literally meets the "pharmaceutical composition" and "pharmaceutically accecptable excipient" limitations of Claim 12, 23, 30 and 31 of U.S. Patent No. 6,939,539. Plaintiff will not call Dr. Arthur H. Kibbe as a witness at trial. Plaintiffs will continue to have the burden of proof regarding all other claim limitations in Claim 12, 23, 30 and 31 of U.S. Patent No. 6,939,539; and Mylan will have the right to argue that it does not meet the remaining claim limitations in Claims 12, 23, 30 and 31. (Signed by Judge Barbara S. Jones on 9/9/2011) (mro) (Entered: 09/12/2011)

09/12/11	202	TRANSCRIPT of Proceedings re: Conference held on 8/30/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Guido Tascione, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/6/2011. Redacted Transcript Deadline set for 10/17/2011. Release of Transcript Restriction set for 12/15/2011.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 09/12/2011)
10/04/11	205	TRANSCRIPT of Proceedings re: Trial held on 9/7/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.

		(Attachments: # 1 transcript)Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	207	TRANSCRIPT of Proceedings re: Trial held on 9/8/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	209	TRANSCRIPT of Proceedings re: Trial held on 9/9/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript

		Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	211	TRANSCRIPT of Proceedings re: TRIAL held on 9/13/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	213	TRANSCRIPT of Proceedings re: TRIAL held on 9/14/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be

viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)

10/04/11 215 TRANSCRIPT of Proceedings re: Trial held on 9/15/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)

10/04/11 217 TRANSCRIPT of Proceedings re:

		TRIAL held on 9/16/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	219	TRANSCRIPT of Proceedings re: Trial held on 9/19/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012. (Attachments: # 1 transcript)Filed In Associated

		Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	221	TRANSCRIPT of Proceedings re: TRIAL held on 9/20/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Linda Fisher, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/04/11	223	TRANSCRIPT of Proceedings re: Trial held on 9/21/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: William Richards, (212) 805-0300. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due

		10/28/2011. Redacted Transcript Deadline set for 11/7/2011. Release of Transcript Restriction set for 1/5/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 10/04/2011)
10/11/11	225	SEALED DOCUMENT placed in vault.(mps) (Entered: 10/11/2011)
10/11/11	226	NOTICE of Materials Filed Under Seal. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Hashmall, David) (Entered: 10/11/2011)
10/17/11	227	POST TRIAL MEMORANDUM. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd..(Solano, Ricardo) (Entered: 10/17/2011)
10/24/11	228	SEALED DOCUMENT placed in vault.(mps) (Entered: 10/24/2011)
10/24/11	229	NOTICE of Materials Filed Under Seal. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Ebie, Kenneth) (Entered: 10/24/2011)

10/26/11	231	PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd..(Hashmall, David) (Entered: 10/26/2011)
10/31/11	232	NOTICE of Materials Filed Under Seal. Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd., Teva Pharmaceutical Industries Ltd., Teva Pharmaceuticals USA, Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Blessing, Carolyn) (Entered: 10/31/2011)
11/01/11	233	SEALED DOCUMENT placed in vault.(nm) (Entered: 11/01/2011)
11/01/11	234	NOTICE of Materials Filed Under Seal. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Ebie, Kenneth) (Entered: 11/01/2011)
11/14/11	237	RESPONSE *to Plaintiffs' Proposed Findings of Fact and Conclusions of*

		Law (redacted). Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Solano, Ricardo) (Entered: 11/14/2011)
11/14/11	238	REPLY *in Support of Post-Trial Findings of Facts and Conclusions of Law.* Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Solano, Ricardo) (Entered: 11/14/2011)
11/15/11	239	PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW. Document filed by Momenta Pharmaceuticals, Inc., Sandoz Inc..Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Doyle, David) (Entered: 11/15/2011)
11/15/11	240	RESPONSE *to Plaintiffs' Proposed Findings of Fact and Conclusions of Law (redacted).* Document filed by Momenta Pharmaceuticals, Inc., Sandoz, Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Doyle, David) (Entered: 11/15/2011)
11/15/11	241	REPLY *to Plaintiffs' Opposition to Sandoz, Inc. and Momenta*

		Pharmaceuticals, Inc.'s Proposed Findings of Fact and Conclusions of Law (redacted). Document filed by Momenta Pharmaceuticals, Inc., Sandoz, Inc.. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(Doyle, David) (Entered: 11/15/2011)
11/16/11	242	RESPONSE *in Opposition to Defendants' Proposed Findings of Fact and Conclusions of Law (Redacted).* Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Hashmall, David) (Entered: 11/16/2011)
11/16/11	243	REPLY *to Defendants' Proposed Findings of Fact and Conclusions of Law (Redacted).* Document filed by Teva Neuroscience, Inc., Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals USA, Inc., Yeda Research and Development Co. Ltd.. (Hashmall, David) (Entered: 11/16/2011)
01/05/12	244	TRANSCRIPT of Proceedings re: Conference held on 11/3/2011 before Judge Barbara S. Jones. Court Reporter/Transcriber: Tara Jones, (212) 805-0300. Transcript may be viewed at the court public terminal

		or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 1/30/2012. Redacted Transcript Deadline set for 2/9/2012. Release of Transcript Restriction set for 4/9/2012.Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(McGuirk, Kelly) (Entered: 01/05/2012)
06/22/12	251	ORDER: After a bench trial and the Court's review of the parties' post-trial briefing, the Court finds that the Defendants', Mylan Pharmaceuticals Inc., et al. and Sandoz, Inc. et al., abbreviated new drug applications infringe all of the asserted claims of the Plaintiffs' patents and that none of the asserted claims are invalid or unenforceable. The full opinion of the Court's findings of fact and conclusions of law will follow immediately after the parties have had the opportunity to review it in order to request redactions of any proprietary information it may contain. See Dkt. No. 332 in 08-cv-7611.) (Signed by Judge Barbara S. Jones on 6/22/2012) Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(laq)

(Entered: 06/22/2012)

06/29/12	252	SEALED DOCUMENT placed in vault.(mps) (Entered: 06/29/2012)
06/29/12	253	OPINION AND ORDER # 102065: For the reasons provided within, the Court finds that both Mylan's and Sandoz's ANDA infringe all of the asserted claims, and that none of the asserted claims are invalid or unenforceable. Teva is ordered to submit a proposed judgment incorporating the rulings contained in this Opinion and Order to the Court on or before July 2, 2012. (Signed by Judge Barbara S. Jones on 6/22/2012) Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ(laq) Modified on 7/16/2012 (ft). (Entered: 06/29/2012)
07/24/12	255	FINAL JUDGMENT that 1. for the reasons set forth in the Court's Opinion dated June 22, 2012, that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE SANDOZ DEFENDANTS with respect to Plaintiffs' claims that the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 nfringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10,12, 23, 30, and 31 ofthe '539 patent, claims 1 and 2 of the '430 patent, and claims

1 and 6 of the '847 patent pursuant to 35 U.S.C. § 271(e)(2)(A), and that each of these asserted claims against the Sandoz Defendants is valid, enforceable, and infringed;2. IT IS FURTHER ORDERED AND. ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE SANDOZ DEFENDANTS with respect to Plaintiffs' declaratory judgment claims pursuant to 35 U.S.C. §§ 2201,2202, that the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 if commercially manufactured, used, marketed, sold, or offered for sale within the United States or imported thereto would infringe claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1 and 2 of the '430 patent, claims 1 and 6 of the '847 patent against the Sandoz Defendants pursuant to 35 U.S.C. §§ 271(a), (b), and (c), and IT IS DECLARED that each of these asserted clai.ms against the Sandoz Defendants is valid, enforceable, and infringed; 3. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and

AGAINST THE SANDOZ DEFENDANTS with respect to the Sandoz Defendants' counterclaims seeking declaratory judgment of non-infringement, invalidity and unenforccability of claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1 and 2 of the '430 patent, claims l and 6 of the '847 patent, claim 1 of the '589 patent, claim 1 ofthe '476 patent, claim 1 of the '161 patent, claim 1 of the '808 patent, and claims 1 and 2 of the '898 patent, all such counterclaims are DISMISSED WITH PREJUDICE, and IT IS DECLARED that each of these asserted claims against the Sandoz Defendants is valid, enforceable, and infringed by the product which is the subject of the Sandoz Defendants' ANDA No. 90-218; 4. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT ISENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE MYLAN DEFENDANTS with respect to Plaintiffs' claims that the product which is the subject of the Mylan Defendants' ANDA No. 91-646 infringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23. 30, and 31 of the '539 patent, claims 1,

2, and 3 of the '430 patent, claims 1 and 6 of the '847 patent, claim l of the '589 patent, claim 1 ofthe '476 patent, and claim 1 of the '161 patent pursuant to 35U.S.C. §271 (e)(2)(A), and that each of these asserted claims against the MylanDefendants is valid, enforceable, and infringed; 5. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT IS ENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE MYLAN DEFENDANTS with respect to Plaintiffs' declaratory judgment claims pursuant to pursuant to 35 U.S.C. §§ 2201, 2202, that the product which is the subject of the Mylan Defendants' ANDA No. 91-646 if commercially manufactured, used, marketed, sold, or offered for sale within the United States or imported thereto would infringe claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims l, 2, and 3 of the '430 patent, claim l of the '589 patent, claim 1 of the '476 patent, claim 1 of the' 161 patent, claims 1 and 6 of the '847 patent against the Mylan Defendants pursuant to 35 U.S.C. §§ 27l(a), (b), (c), and IT IS DECLARED that each of these

asserted claims against the Mylan Defendants is valid, enforceable, and infringed; 6. IT IS FURTHER ORDERED AND ADJUDGED that FINAL JUDGMENT ISENTERED IN FAVOR OF PLAINTIFFS and AGAINST THE MYLAN DEFENDANTS with respect to the Mylan Defendants' counterclaims seeking declaratory judgment of non-infringement invalidity, and unenforceability of claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claims 1, 2, and 3 of the '430 patent, claim 1 of the '589 patent, claim 1 of the '4 7 6 patent, claim 1 of the '161 patent, claim 1 of the '808 patent, claims 1and 6 of the '847 patent, and claims 1, 2, and 3 of the '898 patent, all suchcounterclaims are DISMISSED WIT11 PREJUDICE, and IT IS DECLARED that each of these asserted claimsagainst the Mylan Defendants is valid, enforceable,and infringed by the product which is the subject of the Mylan Defendants'ANDA No. 91-646; 7. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 27l(e)(4)(A), the effective date of any approval by the U.S. Food and Drug Administration ("FDA") of the Sandoz Defendants' ANDA No. 9Q-

218 shall not be earlier than the expiration ofthe '098 patent, the '539 patent, the '589 patent, the '476 patent, the '161 patent, the '430 patent, and the '847 patent on May 24,2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable, the date any such exclusivity ends, but that Plaintiffs will provide written notice to the Sandoz Defendants of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA; 8. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271 (e)(4)(A), the effective date of any approval by the FDA of the Mylan Defendants' ANDA No. 91-646, shall not be earlier than the expiration of the '098 patent, the '539 patent, the '589 patent, the '476 patent, the '161 patent, the '430 patent, and the '847 patent on May 24,2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable, the date any such exclusivity ends, but that Plaintiffs will provide written notice to the Mylan Defendants of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA; 9. IT IS FURTHER ORDERED that,

pursuant to 35 U.S.C. § 27l(eX4)(B), the Sandoz Defendants and each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of the Sandoz Defendants' ANDA No. 90~218, which infringes claims 1 and 8 of the '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, claim 1 of the' 161 patent. claims 1 and 2 of the '430 patent, and claims 1 and 6 of the '847 patent until May 24, 2014; 10. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(B), the Mylan Defendants, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of the Mylan

Defendants' ANDA No. 91-646, which infringes claims 1 and 8 ofthe '098 patent, claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent, claim 1 of the '589 patent, claim 1 of the '476 patent, clahn 1 of the '161 patent, claims 1, 2, and 3 ofthc '430 patent, and claims 1 and 6 of the '847 patent until May 24, 2014; 11. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 283, the Sandoz Defendants, their respective officers, directors, employees, agents, successors, affiliates and assigns, and all persons and entities acting in concert or participation with them are permanently enjoined from directly or indirectly engaging in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Sandoz Defendants' ANDA No. 90-218 until the expiration of the '808 patent on September 1, 2015, and are permanently enjoined from directly or indirectly engaging in the commercialmanufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject ofthe Sandoz Defendants' ANDA No.

90-218 until the expiration of the '098 patent, the '539 patent, the '430 patent, the '589 patent, the '476 patent, the '161 patent, the '847 patent, and the patent '898 patent on May 24, 2014; 12. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 283, the MylanDefendants, their respective officers, directors, employees, agents, successors,affiliates and assigns, and all persons and entities acting in concert or participation with them are permanently enjoined from directly or indirectly engagjng in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Mylan Defendants' ANDA No. 91646 until the expiration of the '808 patent on September 1, 2015, and are permanently enjoined from directly or indirectly engaging in the commercial manufacture, use, marketing, sale, or offer for sale within the United States, or from importing into the United States, of the product which is the subject of the Mylan Defendants' ANDA No. 91-646 until the expiration of the '098 patent, the '539 patent, the '430 patent, the '589 patent, the '476

patent, the '161 patent, the '847 patent, and the patent '898 patent on May 24, 2014; 13. IT IS FURTHER ORDERED THAT nothing in this FINAL JUDGMENT ORDER shall be construed to limit the rights of the parties pursuant to 35 U.S.C. § 27l(e)(l); 14. IT IS FURTHER ORDERED that the Sandoz Defendants and the Mylan Defendants do not waive any rights to appeal any portion of this final judgment including the injunctive relief granted, to the extent the Court's findings or holdings are modified on appeal; and 15. IT IS FURTHER ORDERED that any request for costs pursuant to Fed. R. Civ. P 54(d)(l) and Local Civil Rule 54.1 shall be filed within forty-five (45) days of entry of this FINAL JUDGMENT ORDER, and any motion for attorneys' fees pursuant to Fed. R. Civ. P. 54(d)(2) and 35 U.S.C. § 285 shall be filed within forty-five (45) days of entry of this FINAL JUDGMENT ORDER. The Sandoz Defendants' and the Mylan Defendants' opposition to any request for costs pursuant to Fed. R. Civ. P S4(d)(l) and Local Civil Rule 54.1 shall be filed within ninety (90) days of the filing of such request, and the Sandoz Defendants' and the

		Mylan Defendants' opposition to any motion for attorneys' fees pursuant to Fed. R. Civ. P 54(d)(2) and 35 U.S.C. § 285 shall be filed within ninety (90) days of the filing of such motion. Plaintiffs' reply in support of any motion for attorneys' fees shall be filed within thirty (30) days of the filing of opposition by the Sandoz or Mylan Defendants. (Signed by Judge Barbara S. Jones on 7/23/12) (Attachments: # 1notice of right to appeal)(ml) Modified on 8/1/2012 (jar). (Entered: 07/24/2012)
07/26/12	256	NOTICE OF APPEAL TO THE FEDERAL CIRCUIT from (255 in 1:09-cv-08824-BSJ, 338 in 1:08-cv-07611-BSJ -AJP) Judgment,,,

		and Form 22 are due within 14 days. Document filed by Mylan Inc., Mylan Pharmaceuticals Inc., Natco Pharma Ltd. Filing fee $ 455.00, receipt number 465401044800. Filed In Associated Cases: 1:08-cv-07611-BSJ -AJP, 1:09-cv-08824-BSJ.(tp) (Entered: 07/27/2012)
08/08/12		USCA Case Number 12-1569 from the US Court of Appeals, Federal Circuit assigned to 256 Notice of Appeal to the Federal Circuit, filed by Momenta Pharmaceuticals, Inc., Sandoz Inc.. (nd) (Entered: 08/08/2012)
08/08/12		USCA Case Number 12-1570 from the US Court of Appeals, Federal Circuit assigned to 257 Notice of Appeal to the Federal Circuit, filed by Natco Pharma Ltd., Mylan Inc., Mylan Pharmaceuticals Inc.. (nd) (Entered: 08/08/2012)
07/26/13	262	OPINION of USCA for the Federal Circuit as to (340 in 1:08-cv-07611-BSJ-AJP, 257 in 1:09-cv-08824-BSJ) Notice of Appeal to the Federal Circuit, filed by Natco Pharma Ltd., Mylan Inc., Mylan Pharmaceuticals Inc., (256 in 1:09-cv-08824-BSJ, 339 in 1:08-cv-07611-BSJ-AJP) Notice of Appeal to the Federal Circuit, filed by Momenta Pharmaceuticals, Inc., Sandoz Inc. USCA Case Number

2012-1567, -1568, -1569, -1570. The defendants in these consolidated patent infringement actions (collectively, Appellants) appeal from the district court' judgment that various claims of the nine patents-in-suit asserted by the plaintiffs (collectively, Teva) are infringed, and from the court's holdings regarding indefiniteness, nonenablement, and obviousness. We hold that Group I claims are invalid for indefiniteness, but that Group II claims have not been proven indefinite. We also hold that the district court did not err in its conclusions that the claims are infringed, and that the Appellants failed to prove that the claims would have been obvious and are not enabled. Accordingly, we affirm the district court's judgments of infringement and no invalidity with respect to Group II claims, reverse its judgment of no invalidity with respect to Group I claims, and remand. Jan Horbaly, Clerk USCA for the Federal Circuit. Certified: 07/26/2013. Filed In Associated Cases: 1:08-cv-07611-BSJ-AJP, 1:09-cv-08824-BSJ(nd) (Entered: 07/26/2013)

11/01/13 263 MANDATE of USCA for the Federal Circuit (Certified Copy) as to (340 in

		1:08-cv-07611-BSJ-AJP, 257 in 1:09-cv-08824-BSJ) Notice of Appeal to the Federal Circuit, filed by Natco Pharma Ltd., Mylan Inc., Mylan Pharmaceuticals Inc., (256 in 1:09-cv-08824-BSJ, 339 in 1:08-cv-07611-BSJ-AJP) Notice of Appeal to the Federal Circuit, filed by Momenta Pharmaceuticals, Inc., Sandoz Inc. USCA Case Number 12-1567; 12-1568; 12-1569; 12-1570. In accordance with the judgment (344 Opinion) of this Court, entered July 26, 2013, and pursuant to Rule 41(a)of the Federal Rules of Appellate Procedure, the formal mandate is hereby issued. Jan Horbaly, Clerk USCA for the Federal Circuit. Issued As Mandate: 11/1/2013. (Attachments: # 1 Opinion)Filed In Associated Cases: 1:08-cv-07611-BSJ-AJP, 1:09-cv-08824-BSJ(nd) (Entered: 11/01/2013)
11/18/13		NOTICE OF CASE REASSIGNMENT to Judge William H. Pauley, III. Judge Barbara S. Jones is no longer assigned to the case. (pgu) (Entered: 11/18/2013)
12/16/13	270	CONSENT MOTION to Alter Judgment re: (255 in 1:09-cv-08824-WHP, 338 in 1:08-cv-07611-WHP-AJP)

		Judgment,,,

written notice to Sandoz of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA; 2. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval by the FDA of Mylan's ANDA No. 91-646 shall not be earlier than the expiration of the '098 patent, the '476 patent, the '161 patent, and the '430 patent on May 24, 2014, or, to the extent the FDA determines that a pediatric exclusivity is applicable, the date any such exclusivity ends, but that Plaintiffs will provide written notice to Mylan of such grant of pediatric exclusivity within five (5) days of receiving award of exclusivity from the FDA; 3. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 27l(e)(4)(B), Sandoz and its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of Sandoz's ANDA No. 90-218, until the expiration of the '098 patent, the

'476 patent, the '161 patent, and the '430 patent on May 24, 2014; 4. IT IS FURTHER ORDERED that, pursuant to 35 U.S.C. § 27l(e)(4)(B), Mylan and its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with any of them are permanently enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the product which is the subject of Mylan's ANDA No. 91-646, until the expiration of the '098 patent, the '476 patent, the '161 patent, and the '430 patent on May 24, 2014; and 5. IT IS FURTHER ORDERED THAT nothing in this MODIFIED JUDGMENT shall be construed to limit the rights of the parties pursuant to 35 U.S.C. § 27l(e)(l). (Signed by Judge William H. Pauley, III on 12/20/13) (Attachments: # 1 Notice of Right to Appeal)(ml) (Entered: 12/23/2013)

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs,* v. SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC., *Defendants.*	Civil Action No. 08 CV 7611 (BSJ) (AJP) ECF Case

DECLARATION OF
GREGORY A. GRANT, PH.D.

1. I have been retained by Kenyon & Kenyon LLP to provide my opinions as an expert witness on behalf of Teva Pharmaceuticals USA, Inc., Teva Pharmaceuticals Industries Ltd., Teva Neuroscience, Inc., (collectively, "Teva") and Yeda Research and Development Co. (collectively, "Plaintiffs") regarding U.S. Patents Nos. 5,800,808 ("the '808 patent"),

5,981,589 ("the '589 patent"), 6,048,898 ("the'898 patent"), 6,054,430 ("the '430 patent"), 6,342,476 ("the '476 patent"), 6,362,161 ("the '161 patent"), 6,620,847 ("the '847 patent"), 6,939,539 ("the '539 patent"), and 7,199,098 ("the '098 patent") (collectively, "the patents-in-suit," Exhibit B).

2. I am a professor of Biochemistry in Medicine and of Developmental Biology at the School of Medicine at Washington University in St. Louis, Missouri. I have over 30 years of experience teaching and directing research related to protein and synthetic polypeptide characterization. My own research is focused primarily on the investigation of the regulatory processes of proteins.

3. I have also directed the Protein and Nucleic Acid Chemistry Laboratory (PNACL), an instrumentation core laboratory at Washington University, for over 25 years. In that regard, my staff and I have provided sophisticated analytical and synthetic research capabilities to researchers in the field of protein and synthetic polypeptide chemistry.

4. I have been using size exclusion chromatography ("SEC") and related technologies for over 35 years. I have used this technique to measure the molecular weights of proteins.

5. A copy of my curriculum vitae is attached hereto as Exhibit A, and a short summary follows in section I below.

I. MY BACKGROUND

6. I received a Bachelor of Science in Biochemistry from Iowa State University in 1971. I received a Ph.D. in Biochemistry from University of Wisconsin, Madison in 1975, and conducted three years of postdoctoral research at Washington University School of Medicine.

7. In addition to my academic positions, I have served on several editorial boards for various scientific journals and book series. I have also served on numerous advisory committees and have actively participated in the National Institute of Health, Biochemistry Study Section. In that regard, I have been invited to review federal and state research grant applications and to review academic papers for journal and/or conference publication in the field of biochemistry, protein chemistry, polypeptide science, and biomolecular techniques.

8. I have been invited to present numerous scientific lectures and seminars at conferences, companies, and universities. These lectures and seminars have focused on various aspects of protein analysis, including the instrumentation and techniques for the characterization of proteins and synthetic polypeptides.

9. My research has contributed to the authorship of over 100 peer-reviewed publications and many invited articles/chapters in books, encyclopedias, and scientific journals. Examples of book contributions include chapters in Current Protocols in Protein Science and in Synthetic Peptides: A User's Guide

and entries of synthetic peptides in Encyclopedia of Molecular Biology and Molecular Medicine and in Molecular Biology and Biotechnology: A Comprehensive Desk Reference.

II. FEES

10. My fees for services as an expert witness in this litigation are $500 per hour plus expenses and $750 per hour for deposition and trial testimony. My compensation is not dependent in any way upon the opinions formed or the outcome of this litigation.

III. PRIOR EXPERT TESTIMONY

11. In the last five years (from 2004-2009), I have not testified at a deposition or trial.

IV. MATERIALS CONSIDERED

12. My opinions are based on the patents-in-suit and their prosecution histories[1], the materials identified in the Declaration, my knowledge, education, and experience, and the materials listed in Exhibit C.

V. SUMMARY OF EXPECTED TESTIMONY

13. I have been informed that the Plaintiffs filed the present lawsuit against Sandoz, Inc., Sandoz International GMBH, Novartis AG, and Momenta

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[1] I understand that the correspondence between the patent applicants and the United States Patent and Trademark Office ("the Patent Office") leading to the issuance of the patent is called the prosecution history of that patent.

Pharmaceuticals, Inc. (collectively, "Defendants") on the basis that Defendants infringe the claims of the patents-in-suit.

14. If called as a witness, I expect to testify on the following topics and to provide opinions and testimony on what is summarized in this Declaration:

a. The state of the art at times relevant to the subject matter set forth below;

b. The level of ordinary skill in the art to which the patents-in-suit are directed;

c. The patents-in-suit, their specification and claims, the science underlying what is disclosed in the patents-in-suit, the interpretation of the claims of the patents-in-suit by the person of ordinary skill in the art to which the patents-in-suit are directed; and

d. My opinions about how certain terms and phrases in the claims of the patents-in-suit should be interpreted by a person of ordinary skill in the art.

VI. THE PATENTS-IN-SUIT

15. The patents-in-suit, all of which are entitled "Copolymer-1 Improvements in Compositions of Copolymers," generally relate to low molecular weight copolymer-1 and methods of making low molecular weight copolymer-1. The patents-in-suit have essentially the same specification ("the specification"), but have different claims.

16. Copolymer-1 was developed by three of the inventors of the patents-in-suit (Michael Sela, Dvora Teitelbaum, and Ruth Arnon) and their co-workers many years prior to the filing of the applications for the patents-in-suit. The prior art copolymer-1 is described in the patents-in-suit as having average molecular weights of 23,000 daltons (e.g., the '808 patent, col. 1, lines 34-37). The patents describe copolymer-1 of lower molecular weight than the original copolymer-1. In addition, the patents describe methods of making copolymer-1 of lower molecular weight (e.g., patents-in-suit, Examples 1, 3, and 4) and the use of lower molecular weight copolymer-1 to treat multiple sclerosis (e.g., the '808 patent, col. 1, lines 51-53 and col. 2, lines 47-48).

17. The patents describe the characteristics of low molecular weight copolymer-1, which include, for example, the average molecular weight of the copolymer-1 and the percentage of the species within a certain molecular weight range (e.g., the '808 patent, col. 1, line 64-col. 2, line 14). In Example 1, the patents describe that the molecular weight distribution of copolymer-1 was determined on a calibrated gel filtration column. The molecular weight distributions of copolymer-1 batches are illustrated in Figures 1 and 2.

VII. LEVEL OF ORDINARY SKILL IN THE ART

18. I understand that patent claims are to be interpreted from the point of view of a person of ordinary skill in the relevant art in view of the description of the invention in the patent.

19. I have reviewed the specifications, claims, and relevant portions of the prosecution histories of the patents-in-suit.

20. I understand that the relevant time period for the person of ordinary skill in the art to interpret the claim terms is the filing date of the patent. I also understand that each of the patents-in-suit, although filed on different dates, claim priority to a continuation-in-part application filed May 22, 1995, which in turn claims priority to applications filed November 23, 1994 and May 24, 1994.

21. Based on my experience, it is my opinion that a person of ordinary skill in the art of the patents-in-suit would have had an advanced degree or equivalent in a chemical or biological discipline, and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides. In my experience, this person of skill in the art would also have had access to and the ability to consult with other scientists having related and/or complementary knowledge and experience in the areas of polymer chemistry, biochemistry, analytical chemistry, separation technology, medicine, and toxicology.

VIII. BACKGROUND POLYPEPTIDE AND MOLECULAR WEIGHT PRIMER

A. MOLECULE, MOLECULAR WEIGHT, AND MOLAR FRACTION

22. An atom is the smallest unit of a chemical element, having all the characteristics of that

element. The mass of an atom is often expressed using a unit called dalton (Da). A dalton is defined as 1/12 of the mass of a carbon atom. Each atom of a chemical element has a unique atomic weight[2] For example, the most common form of the hydrogen atom has an atomic weight of 1, of carbon, 12, of nitrogen, 14, and of oxygen, 16.[3]

23. A molecule is the smallest unit of a chemical substance that still displays the properties associated with that substance. Molecules may contain two atoms of the same element, such as oxygen (O_2), which has two oxygen atoms, or they may consist of two or more different atoms, such as water (H_2O), which has two hydrogen atoms and one oxygen atom.

24. The molecular weight of a molecule is calculated by adding the atomic weights of the atoms in the molecule. For example, the molecular weight of a water (H_2O) molecule is calculated by adding the atomic weights of two hydrogen atoms and one oxygen atom (1+1+16=18).

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[2] Although relative atomic and molecular weights are dimensionless quantities, in my experience, these quantities are often referred to as having a mass in daltons, e.g., an atomic weight or a molecular weight of x daltons.

[3] The atoms of an element may exhibit different atomic weights. Atoms of the same element which differ in atomic weight are called isotopes. For example, carbon can exist as isotopes having atomic weights of 12 (most common), 13 (far less common), or 14 (even less common). For the remainder of this report, when referring to the atomic weight of an element, I will make reference to the most common form of that element.

25. A mole is defined as the quantity of a substance that has the same number of molecules as found in 12 grams of carbon-12. One mole of a substance always contains 6.022×10^{23} molecules, which has a weight in grams that equals the molecular weight of that substance. For example, water has a molecular weight of 18, the mass of a water molecule is 18 daltons, and therefore one mole of water has a weight of 18 grams.[4]

26. In expressing the composition of a mixture, molar fraction refers to the number of moles of a particular component in the mixture divided by the total number of moles of all components in the mixture. Because the number of molecules in one mole of any substance is always 6.022×10^{23}, molar fraction is also equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Similarly, molar ratio refers to the ratio of the number of moles of each component in a mixture, which is equivalent to the ratio of the number of molecules of each component in a mixture.

B. AMINO ACIDS AND POLYPEPTIDES

27. Amino acids are the basic building blocks of proteins. Each amino acid molecule contains: (1) an amino group, NH_2; (2) a carboxylic acid (carboxyl) group, COOH, and; (3) another chemical group referred to as a side chain represented by R in the formula shown in Figure A below.

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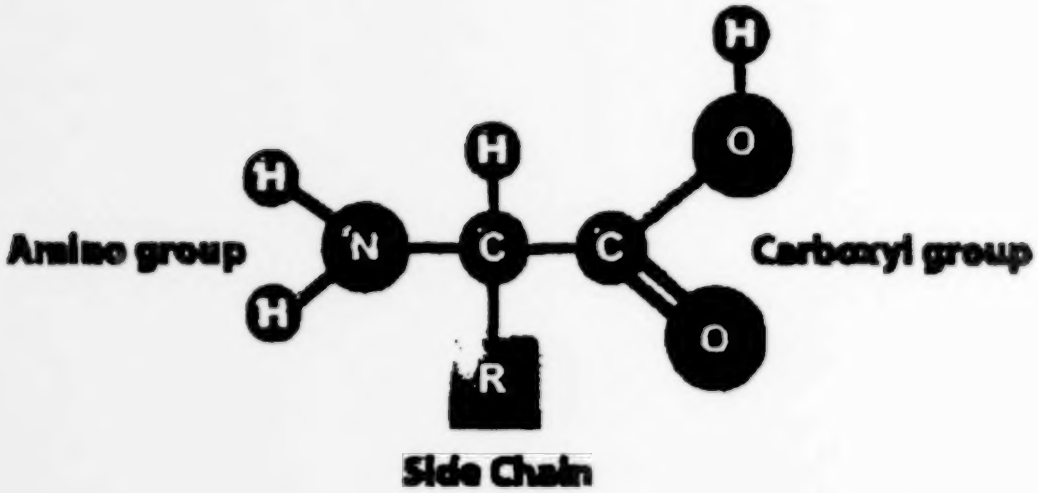
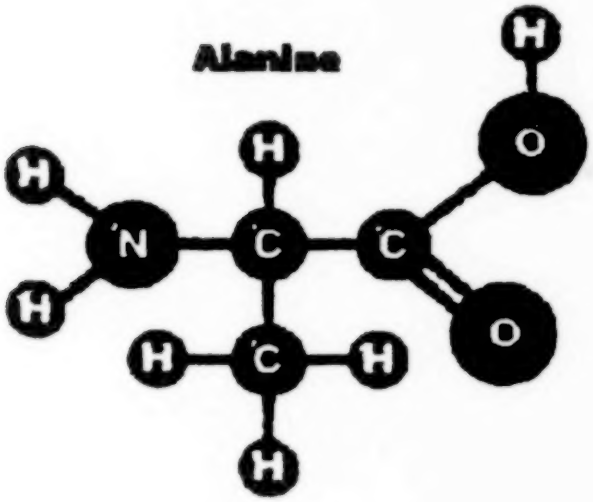
[4] In my experience, the terms "weight" and "mass' are used interchangeably.

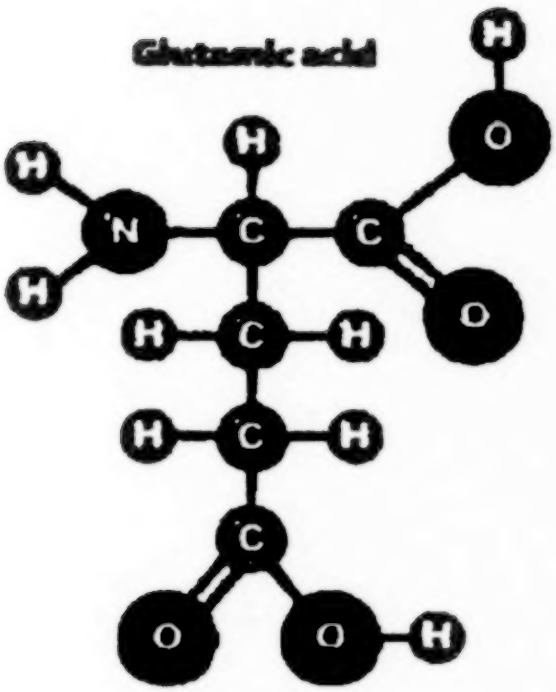
Figure A. Amino Acid

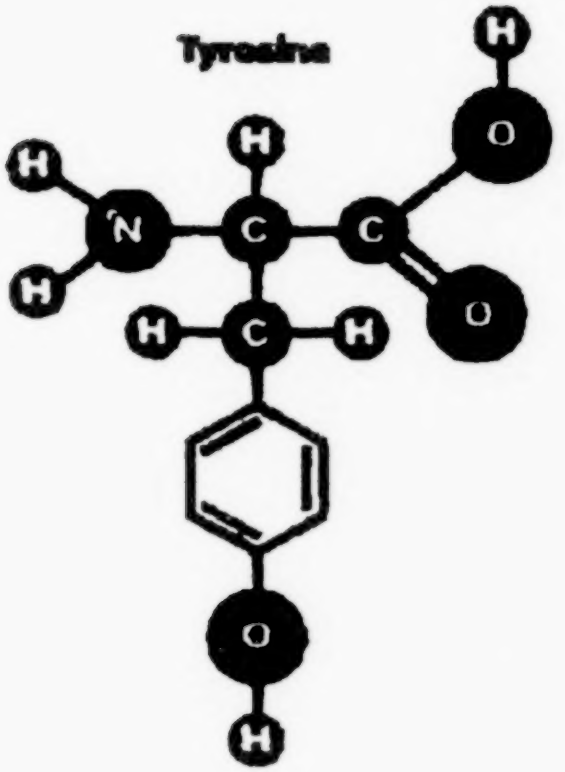


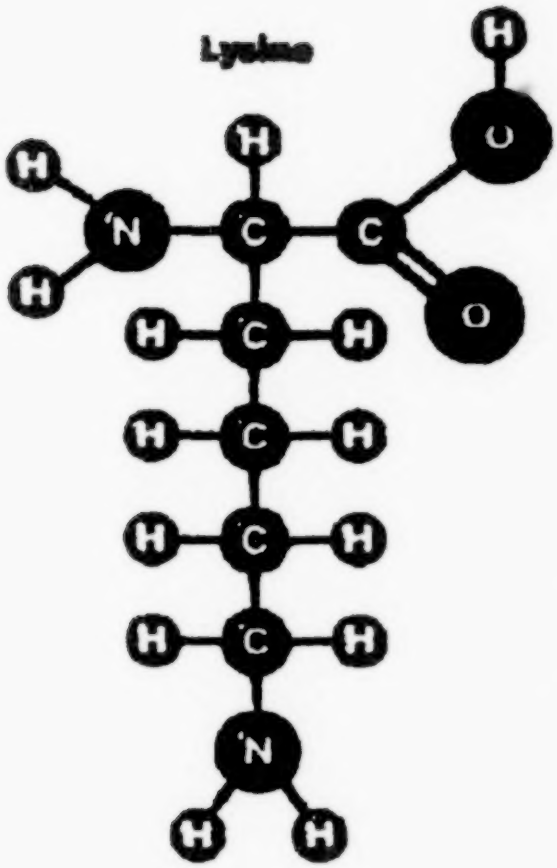
28. There are twenty different genetically-coded amino acids that make up proteins in mammals, each with a different R-group. For example, the simplest amino acid is glycine, with the R-group being a hydrogen atom. The R-groups of alanine, glutamic acid, lysine, and tyrosine are shown in the formulas in Figure B below.

Figure B. Alanine, Glutamic acid, Lysine, and Tyrosine



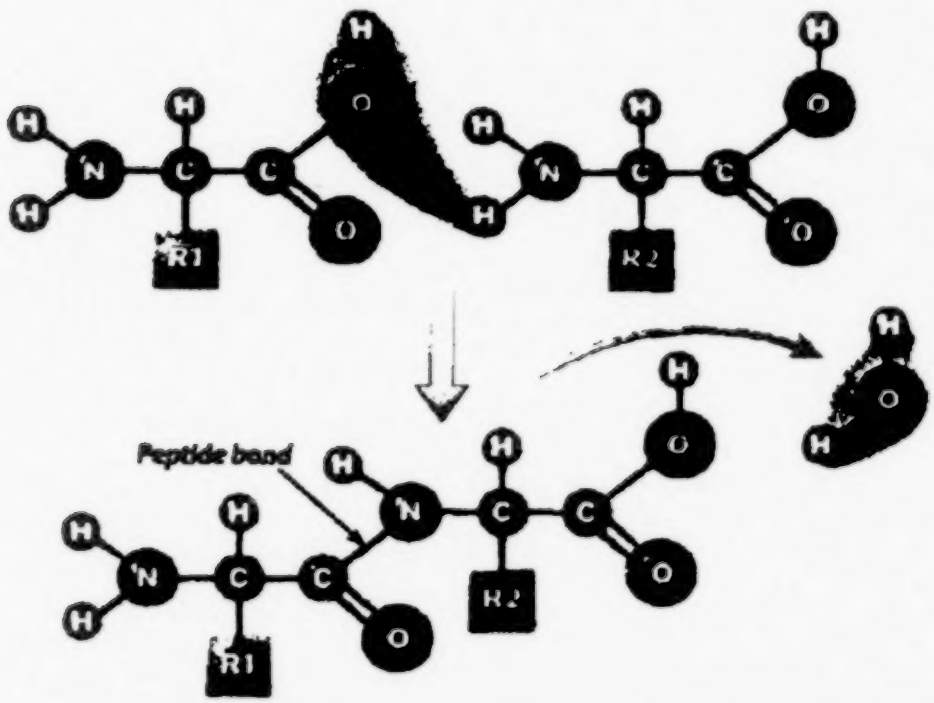



Tyrosine
H
O
H
N
C
C
H
O
H
C
H
O
H


Lysine
H
O
H
N
C
C
H
O
H
C
H
H
C
H
H
C
H
H
C
H
H
C
H
N
H
H

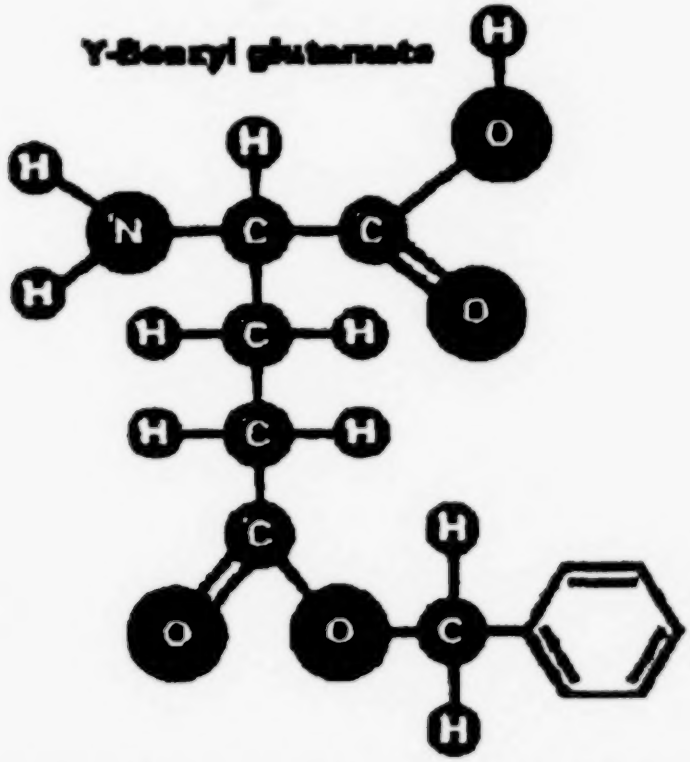
A peptide bond is a linkage between two amino acids that is formed when the amino group of one amino acid reacts with the carboxyl group of another amino acid. Polypeptides are chains of amino acids held together by peptide bonds. Generally, peptide bonds form as shown in Figure C below.

Figure C. Formation of a peptide bond



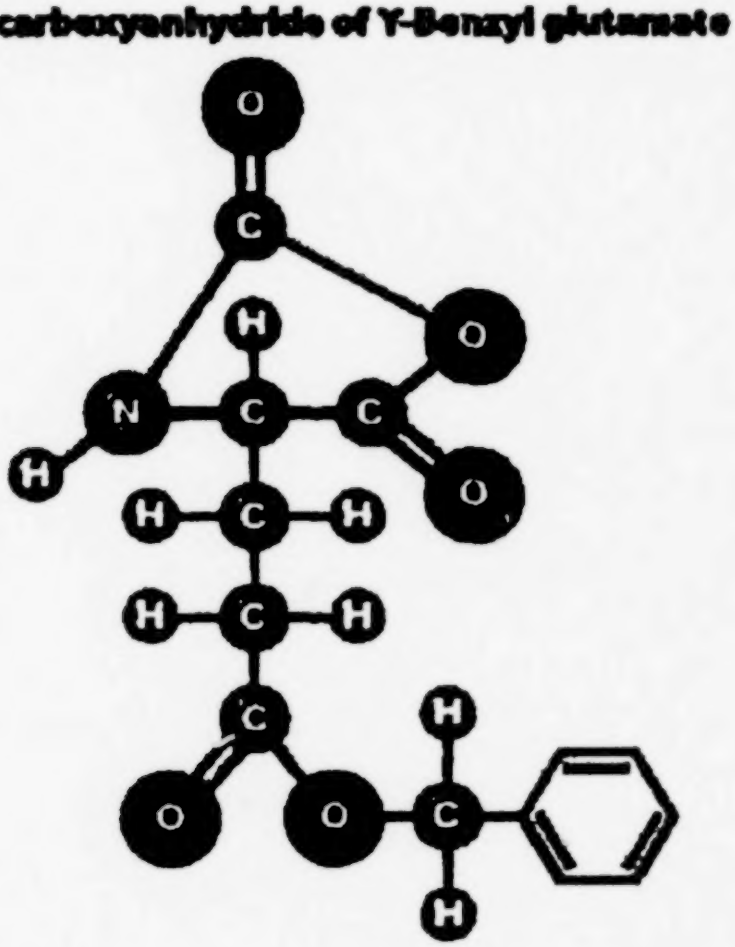
29. In some cases, the R-groups of some amino acids contain chemical groups that are potentially reactive chemical group is achieved by chemically modifying it so that it is no longer reactive. The process of chemical modification is sometimes called "protecting" and the chemical modification is called a "protecting group" After the polypeptides are formed, these protecting groups can be removed. For example, a protected glutamic acid is shown in Figure D below.

Figure D. Protected glutamic acid



30. As amino acids themselves generally have low reactivity, in protein biosynthesis the reactions between amino acids are facilitated by enzymes. To facilitate the chemical synthesis of polypeptides, amino acids are converted into a more "reactive" form first. One example of a reactive form of an amino acid is the formation of a carboxyanhydride that links the α-amino and the α-carboxyl groups, forming an N-carboxyanhydride, or NCA, of the corresponding amino acid. For example, the NCA of a protected glutamic acid is shown in Figure E below.

Figure E. NCA of protected glutamic acid



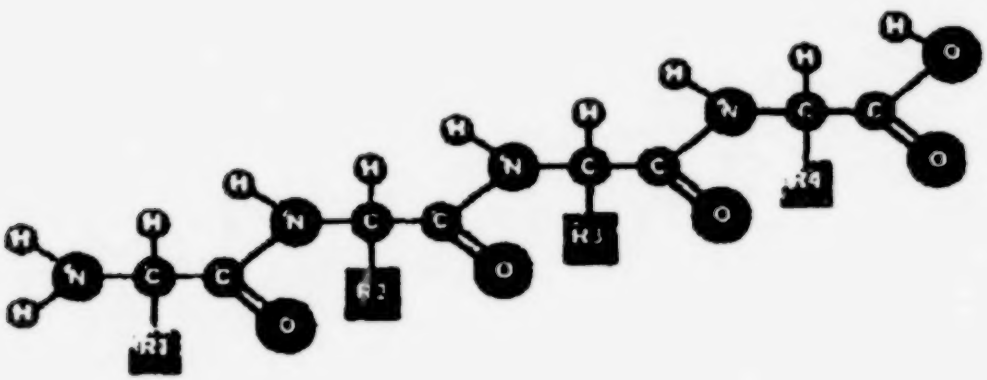
31. When these amino acid NCAs are mixed together, they can be activated by an initiator, and this will cause them to react with each other to form polypeptides. A commonly used initiator for this reaction is an amine such as diethylamine.

C. COPOLYMER-1

32. A polymer molecule is a molecule composed of monomers[5].

A copolymer is a polymer composed of more than one type of monomer.

For example, a polypeptide made of more than one type of amino acid monomer is a copolymer.



33. When several different monomers are allowed to react with each other to form a polymer or copolymer, they can react in any order and to a greater or lesser extent. Such polymerization reactions therefore often result in molecules comprised of various numbers of monomers (and hence various sizes).

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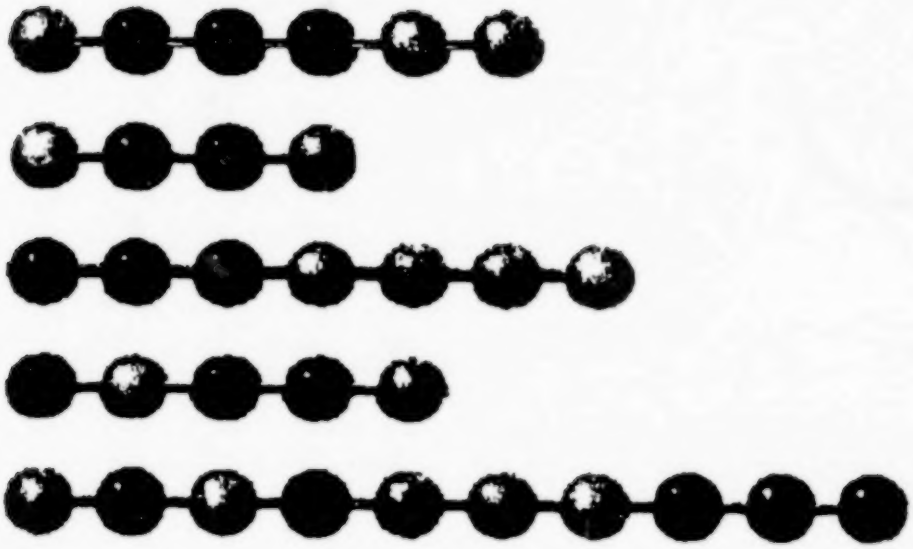
[5] An amino acid, for example, is a monomer.



Therefore, the terms "polymer" and "copolymer" are often used to refer to a collection of molecules with non-uniform sizes, and non-uniform orders of monomers.[6]

34. Copolymer-1 is a name given by its developers to a specific kind of copolymer made of four amino acids, namely alanine, glutamic acid, lysine, and tyrosine. The original copolymer-1 was synthesized by the method described in U.S. Patent No. 3,849,550 ("the '550 patent," attached as Exhibit D) and Teitelbaum *et al.*, Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide, *Eur. J. Immunol.*, 1971. 1: 242-248 ("Teitelbaum," attached as Exhibit E). The method described in the prior art involves:

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[6] The order of monomers in a polymer is sometimes referred to as the "sequence", especially when such monomers are amino acids.

i. Polymerization to make protected copolymer-1: polymerizing the NCAs of alanine, γ-benzyl-protected glutamic acid, and trifluoroacetyl-protected lysine, and tyrosine, in a molar ratio of about 5: 2: 4: 1[7], at room temperature in anhydrous dioxane with diethylamine as the initiator (see Exhibit E, Teitelbaum, p. 243, § 2.3.1);

ii. Debenzylation to make trifluoroacetyl copolymer-1: removing the γ-benzyl protecting groups on the glutamic acid residues by treating the protected copolymer-1 from step i with hydrogen bromide in glacial acetic acid (see Exhibit E, Teitelbaum, p. 243, § 2.3.1); and

iii. Making copolymer-1: removing the trifluoroacetyl protecting groups on the lysine residues by treating the trifluoroacetyl copolymer-1 with 1M piperidine (see Exhibit E, Teitelbaum, p. 243, § 2.3.1).

The alanine, glutamic acid, lysine, and tyrosine in the resulting copolymer-1 have a molar ratio of about 6: 2: 5: 1 (see Exhibit E, Teitelbaum, p. 243, Table 1). Teitelbaum describes the resulting copolymer-1 as having a molecular weight of 23,000 (see Exhibit E, Teitelbaum, p. 242, Abstract).

35. The patents-in-suit describe that copolymer-1 of lower molecular weight can be obtained by either

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[7] See Exhibit E, Teitelbaum, p. 243, Table 1.

removing undesired high molecular weight species or using a different reaction time and/or temperature that had been described for the debenzylation step (e.g., the '808 patent, col. 2, lines 29-40). As described in the patents-in-suit, such lower molecular weight copolymer-1 showed lower negative effects in a mouse mortality and/or an RBL degranulation test. See Example 2 of the patents-in-suit.

D. MOLECULAR WEIGHT OF POLYMERS

36. Because a polymer composition often includes molecules of varying weights, the molecular weight of such a polymer cannot be characterized by the molecular weight of any single species. The most precise way of describing the molecular weight of such a polymer is a complete molecular weight distribution, i.e., knowledge of the mole or weight fraction of each species. See Flory, Principles of Polymer Chemistry, 1953, p. 317 (attached as Exhibit F). However, for purposes of simplicity and practicality, the molecular weight of a polymer is often expressed in a single, average molecular weight.

37. There are many ways to analyze the molecular weight of a polymer. The molecular weight of a polymer can be measured using methods such as osmometry, light scattering (also known as "MALLS[8]"), ultracentrifugation, mass spectrometry, such as MALDI[9]. Alternatively, the polymer can be

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[8] Multi-Angle Laser Light Scattering

[9] Matrix-Assisted Laser Desorption Ionization

separated into fractions, each with a narrow size distribution, using methods such as size exclusion chromatography ("SEC", also known as gel permeation chromatography ("GPC") or gel filtration chromatography). Thereafter, the molecular weight of each fraction is measured directly using the methods referred to above, or measured indirectly by comparing them to polymer standards for which molecular weights have previously been determined.

38. Depending on the methods used, the molecular weight obtained may represent different types of average molecular weight. For example, when a sample of a polymer is measured by osmometry, the molecular weight obtained is a number average molecular weight (commonly referred to as "M_n"), which represents the total weight of the sample divided by the total number of moles of molecules which it contains. On the other hand, when a sample of a polymer is measured by MALLS, the larger molecules will make a greater contribution to the light scattering than an equal weight of smaller ones, and the molecular weight obtained is a weight average molecular weight (commonly referred to as "M_w"). In a sample containing non-uniform molecular species, M_w is always larger than M_n because the larger molecules are "weighted" more heavily in the weight averaging.

39. When a sample of a polymer is analyzed by size exclusion chromatography, a molecular weight distribution will be obtained, and the molecular weight at the highest point of the resulting

chromatogram[10] is referred to as the peak molecular weight, or peak average molecular weight (commonly referred to as "M_p"). The values for M_n and M_w can be further calculated using the size exclusion chromatography data. Unlike M_n and M_w, M_p does not require additional calculation and can be read directly from a chromatogram in combination with a calibration curve.

E. SIZE EXCLUSION CHROMATOGRAPHY (SEC)

40. The patents describe the use of a calibrated gel filtration column to determine the molecular weight distribution of copolymer-1. See Example 1 of the patents-in-suit. SEC was well understood at the time the patent applications were filed in 1994. Typically, SEC is performed by passing a solution of a polymer down a column packed with a porous gel, which separates the polymer into fractions based on its hydrodynamic properties, which are commonly equated to molecular size. The gel particles in the column contain pores of a predetermined size range. Smaller molecules more easily diffuse into these pores and therefore are retarded to a greater extent than larger molecules. Larger molecules bypass the small pores and come out of the column earlier (having lower elution volume). The elution volume, or retention time at constant flow rate, is directly related to the hydrodynamic size of the molecules, which is in turn related to molecular weight. The

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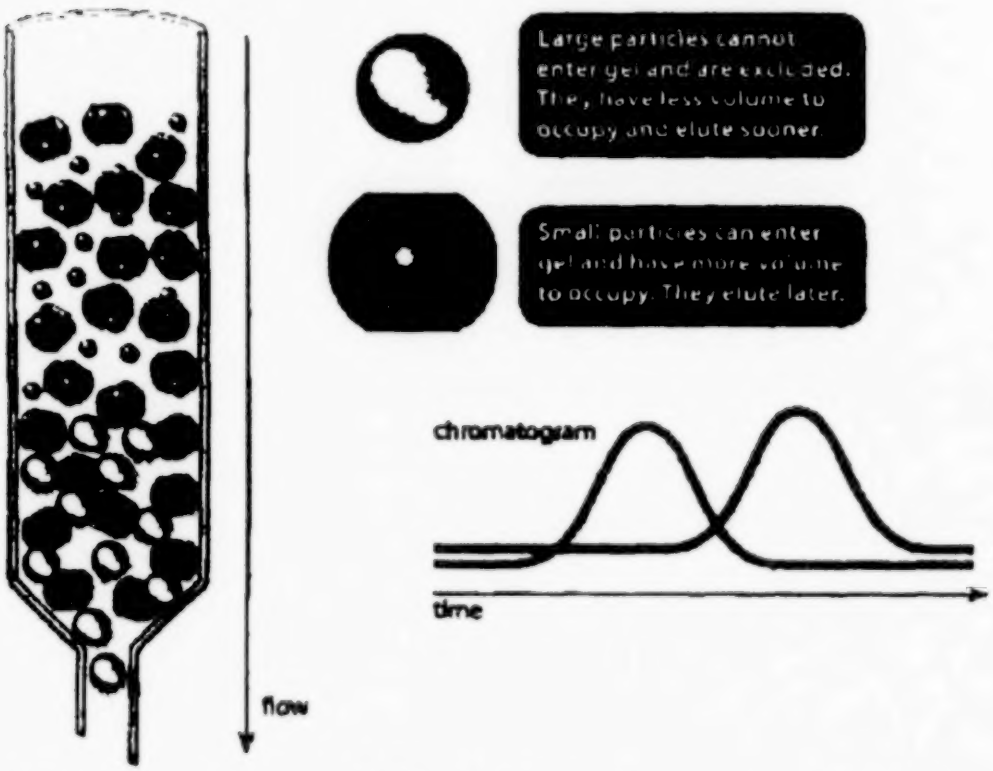
[10] A chromatagram is the visual output of the size exclusion chromatography procedure.

concept of SEC is illustrated using two different uniform-sized molecules in Figure F below.

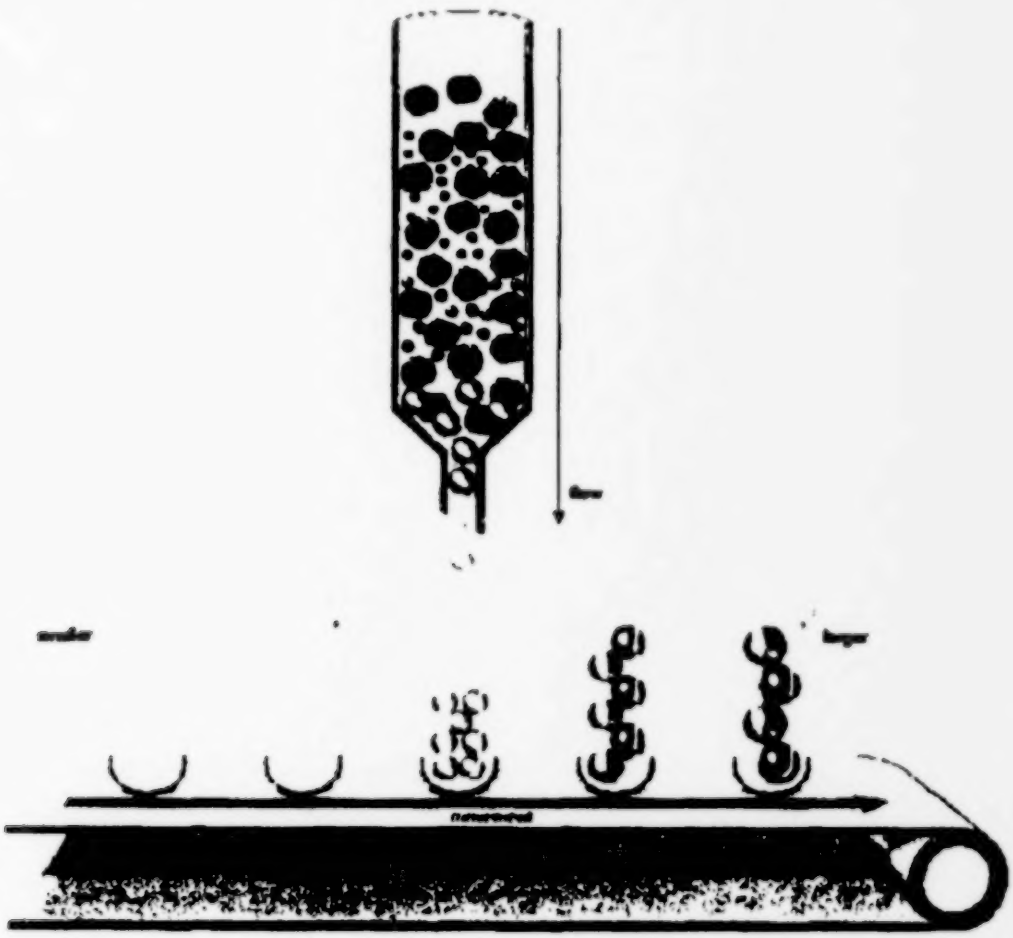
Figure F Size Exclusion Chromatography



41. Thus, through SEC, the polymer molecules are separated into multiple fractions, each including molecules of a certain size that come out at a certain elution volume, as shown in Figure G below.[11]

[11] Each fraction includes molecules that come out in a discrete volume range. For practical purposes, the molecules within each fraction are treated as if they have the same size.

Figure G. Separating molecules using SEC



The total amount of the molecules within each fraction can be determined through the measurement of an optical response such as ultraviolet ("UV") absorbance.[12] A chromatogram is generated by plotting UV absorbance versus elution volume or retention time. The peak on the chromatogram corresponds to a fraction that contains the largest amount of polymer, the molecular weight of which is the peak or "peak

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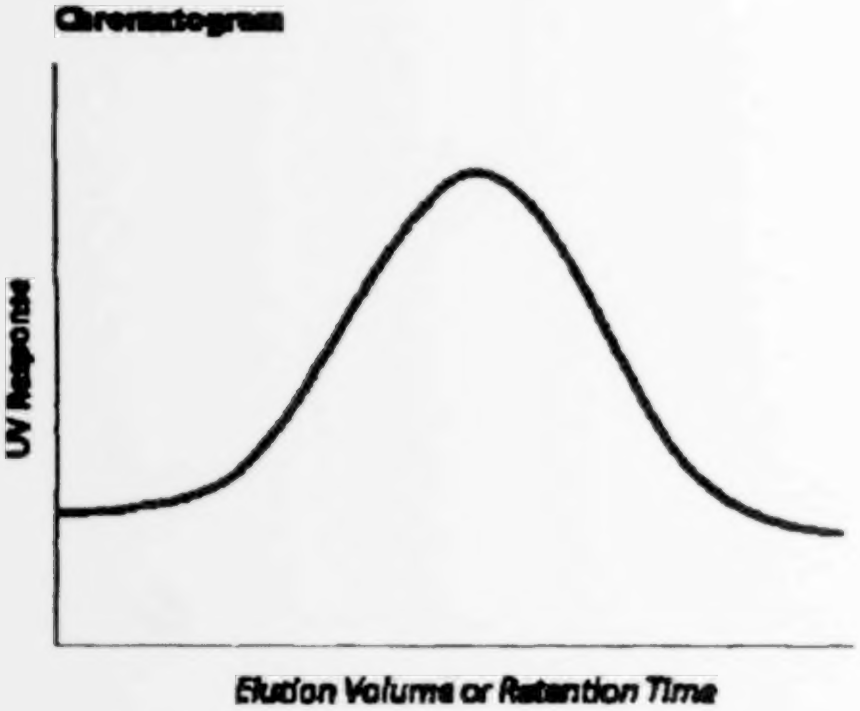
[12] For example, UV absorption at 275 nm detects the amount of tyrosine in a fraction. Assuming that the overall ratio of tyrosine in the polypeptides is constant, the UV absorption is proportional to the amount of all polypeptides in that fraction.

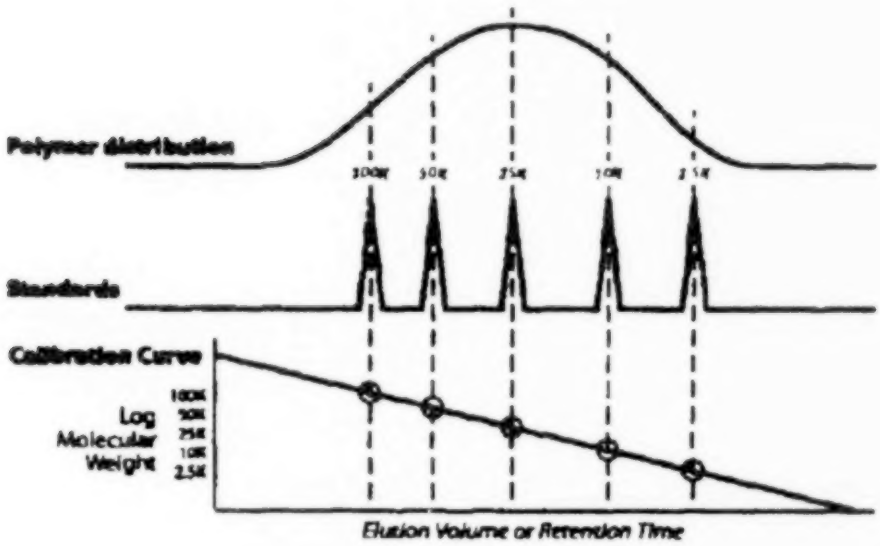
average molecular weight. A typical chromatogram of a polymer is shown in Figure H below.

Figure H. Typical SEC chromatogram



42. The molecular weight of the molecules in each fraction can be directly measured using the methods described above, thereby obtaining the molecular weight distribution of the polymer. An easier and more common method, however, is to correlate the elution volume or retention time on the chromatogram to molecular weight through standards that have known molecular weights. This process is also called column calibration. Through the process of column calibration, a calibration curve can be generated by plotting the molecular weights of standards against their elution volumes or retention times, as shown in Figure I below.

Figure I. Calibration of SEC column



With a calibration curve in place, the molecular weight corresponding to any elution volume or retention time, including the peak average molecular weight, can be read directly off the calibration curve.

43. With a chromatogram and a proper calibration curve, the peak average molecular weight of a polymer can be read without any further calculation. The calibration can also be used to convert the chromatogram into a molecular weight distribution curve.

IX. CLAIM CONSTRUCTION

44. In the paragraphs that follow, I set forth my opinion as to the proper interpretation of phrases or terms in the claims of the patents-in-suit by the person of ordinary skill in the art to which the claims of the patents are directed.

45. I understand that Teva is asserting claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1-6 of the '898 patent, claims 1-6 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1-8 of the '847 patent, claims 1-33 of the '539 patent, and claims 1-14 and 19-20 of the '098 patent.

A. Copolymer-1

46. The term "copolymer-1" is defined in the specification. Specifically, the specification describes copolymer-1 as "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6: 2: 5: 1, respectively." See the '808 patent, col. 1, lines 32-34. The specification states that the copolymer-1 that had been known in the prior art had a higher molecular weight than the copolymer-1 described in the patents. Referencing the '550 patent, the patents state that the prior art copolymer-1 had "average molecular weights of 23,000 daltons." See the '808 patent, col. 1, lines 34-37. A person of skill in the art would have understood from the specification that the invention of the patents involves, in part, copolymer-1 of lower molecular weight than had been described in the prior art. Also, during the prosecution of the '539 patent, the applicants explained to the Patent Office that copolymer-1 is not limited to a specific average molecular weight. See the '539 patent prosecution history, 12/1/2004 Amendment (attached as Exhibit G), page 9 [TEV000304802]. It is my opinion that a person of skill in the art would have understood that the term "copolymer-1" as used in the patents is not limited to any particular molecular weight.

47. A person of skill in the art would have understood that copolymer-1 is made by a process in which the four carboxyanydride amino acids are mixed together with no external guidance as to the amino acid sequence of the resulting polypeptides. However, because each of the four amino acids has a unique structure and reactivity, the formation of the peptide bonds among these amino acids is dictated to some degree by the chemical properties of the amino acids and their reactivities for one another. Thus, a person of skill in the art would have understood that the polymerization is not random in a statistical sense.[13]

48. A person of skill in the art would have understood that the specific amino acid sequence and the number of amino acids in any given polypeptide making up copolymer-1 cannot be predicted because of the complex nature of the interactions among the four amino acids. The result of the above polymerization is a complex mixture of many polypeptide species. Although it is possible that some of the polypeptide species might happen to have the same amino acid makeup (sequence and number of residues), a person of skill in the art would have understood that the mixture, as a whole, is non-uniform with respect to amino acid sequence as well as the number of amino acid residues. Because the molecular weight of a polypeptide is the

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[13] In statistics, "random" is defined as "governed by or involving equal chances for each of the actual or hypothetical members of a population." See entry of "random" in Oxford English Dictionary Online, Second Edition, 1989 (attached as Exhibit H), B.1.b.

sum of its amino acid residues, a person of skill in the art would have understood that the polypeptides comprising copolymer-1 are also non-uniform with respect to molecular weight.

49. Examples 3 and 4 of the patents-in-suit, as well as the references cited therein, clearly explains that copolymer-1 is synthesized by polymerizing the carboxyanhydrides of four amino acids and protected amino acids. See Exhibit E, Teitelbaum, p. 243, section 2.3.1.

50. Therefore, in my opinion, the term "copolymer-1" would have been understood by a person of skill in the art to mean "a complex mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6: 2: 5: 1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides."

B. Copolymer-1 composition

51. The term "composition" in the context of the patents-in-suit has an ordinary meaning of "a product of mixing or combining various elements or ingredients." See Webster's Ninth New Collegiate Dictionary, 1988, p. 270 (attached as Exhibit I). In the context of copolymer-1, copolymer-1 itself can be a composition because it includes polypeptides of various sizes. Further, by definition the composition can also include other components. Thus, in my opinion, the term "copolymer-1 composition" would have been understood by a person of skill in the art

to mean "copolymer-1, optionally in combination with other substances."

C. Polypeptides composed of glutamic acid, lysine, alanine and tyrosine

52. The plural "polypeptides" refers to more than one polypeptide. Also, the term "polypeptides" in its corresponding claim (claim 1 of the '539 patent) refers to copolymer-1. A person of skill in the art would have understood that the polypeptides of copolymer-1 are synthesized by polymerization of suitably protected amino acid carboxyanhydrides, and that such chemical polymerization would inherently result in polypeptides that contain at least some impurities besides the four amino acid residues. The impurities would include, for example, amino acids having unremoved protecting groups and/or initiator groups. While these impurities do not materially affect the underlying characteristics of the polypeptides, they are inevitably present in the polypeptides. As such, the term "polypeptides composed of glutamic acid, lysine, alanine and tyrosine" would have been understood by a person of skill in the art to mean "more than one polypeptide, each of which contains glutamic acid, lysine, alanine, and tyrosine residues." The person of skill would not have found it reasonable to interpret this phrase in a way that would exclude the inevitable impurities of the polymer formation process.

D. Copolymers of alanine, glutamic acid, lysine and tyrosine

53. The plural "copolymers" refers to more than one copolymer. Also, the term "copolymers" in its corresponding claim (claim 1 of the '098 patent) refers to copolymer-1. A person of skill in the art would have understood that the copolymers of copolymer-1 are synthesized by polymerization of suitably protected amino acid carboxyanhydrides, and that such chemical polymerization would inherently result in copolymers that contain at least some impurities. For essentially the same reasons stated in paragraph 52, it is my opinion that the term "copolymers of alanine, glutamic acid, lysine and tyrosine" would have been understood by a person of skill in the art to mean "more than one polymer molecule, each of which contains glutamic acid, lysine, alanine, and tyrosine residues." The person of skill would not have found it reasonable to interpret this phrase in a way that would exclude the inevitable impurities of the polymer formation process.

E. Molecular weight

54. In my opinion, the term "molecular weight," unmodified by terms that would imply an average molecular weight, such as when referring to individual molecular species, would be understood by a person of skill in the art to have its ordinary meaning of "the sum of the atomic weights of the atoms making up a molecule."

F. Copolymer-1 having a molecular weight

55. The person of skill in the art would have understood that because copolymer-1 is a mixture of polypeptides that are non-uniform with respect to molecular weight, it cannot have "a" molecular weight. A person of skill in the art would have understood that "copolymer-1 having a molecular weight" means copolymer-1 having an average molecular weight.

56. Further, in the context of claim 1 of the '808 patent and claim 1 of the '589 patent, where the term appears, the copolymer-1 recited in the claims has a molecular weight of about 5 to 9 kilodaltons. This molecular weight range coincides with the "7000 ± 2000 Da" disclosed in Example 4 of the specification. See the '808 patent, col. 4, lines 62-65 and col. 5, lines 3-5. A person of skill in the art would have understood that copolymer-1 prepared according to the method of Example 4 would include species that have individual molecular weights that are either below or above the range of about 5 to 9 kilodaltons. Therefore, a person of skill in the art would not have understood the term "molecular weight" to mean the individual molecular weight of all species within the copolymer-1.

57. Therefore, in my opinion, the term "copolymer-1 having a molecular weight" would have been understood by a person of skill in the art to mean "copolymer-1 having an average molecular weight," which further means "copolymer-1 having a peak molecular weight detected using an appropriately calibrated suitable gel filtration column." See

paragraph 66 for interpretation of "average molecular weight."

G. Molecular weight range

58. The ordinary meaning of the term "range" is "a set of values between an upper boundary and a lower boundary." Therefore, in my opinion, the term "molecular weight range" would have been understood by a person of skill in the art to mean "a set of molecular weights between an upper boundary and a lower boundary."

H. Molecular weight profile

59. The term "molecular weight profile" appears in col. 2, lines 29-30 and 36-40 in the '808 patent and in the context of "copolymer-1 with the desired molecular weight profile." Viewed in the context of the Specification, the paragraph in which the term appears follows the first three paragraphs under Detailed Description of the Invention. In these three paragraphs, the characteristics of the copolymer-1 of the invention are described in various ways, for example, in certain percentages of species having a molecular weight above a certain level, in having certain percentage of the polymer molecules within a certain molecular weight range, and in having an average molecular weight within certain ranges. See the '808 patent, col. 1, line 64-col. 2, line13. The specification also provides actual examples of how copolymer-1 with these molecular weight characteristics can be made. Therefore, the "desired molecular weight profile" should be interpreted to include all of the aforementioned molecular weight

characteristics, and the term "molecular weight profile" would have been understood by a person of skill in the art to mean "molecular weight characteristics of a sample."

I. Molecular weight distribution

60. In his polymer chemistry textbook, Flory defines molecular weight distribution as "knowledge of the mole or weight fraction of each species." See Exhibit F, Flory, Principles of Polymer Chemistry, 1953, p. 317. This definition is equivalent to "a description of the relationship between the quantity of molecules and the molecules' respective molecular weights," which would be what a person of skill in the art would have understood the term "molecular weight distribution" to mean. This understanding is supported by the use of the term in the claims and the specification. For example, the specification refers to Figures 1 and 2 as showing a molecular weight distribution. See the '808 Patent, col. 1, lines 56-59. The figures provide "a description of the relationship between the quantity of molecules and the molecules' respective molecular weights." Thus, the term "molecular weight distribution" would have been understood by a person of skill in the art to mean "a description of the relationship between the quantity of molecules and the molecules' respective molecular weights."

J. Average molecular weight

61. Example 1 of the specification states that the molecular weight distribution of copolymer-1 was determined on a calibrated gel filtration column,

specifically a Superose 12 column, using a UVIKON spectrophotometer. See the '808 Patent, col. 3, lines 3-8. As such, a person of skill in the art would have understood that the method of determining molecular weight distribution was size exclusion chromatography, and that a calibration curve was generated to correlate molecular weight with elution volume or retention time. Example 1 also describes the average molecular weights of the batches that were analyzed by SEC. I note that peak molecular weight, also called peak average molecular weight, is the molecular weight at the highest point of a chromatogram. Peak molecular weight can be obtained directly from the chromatogram and the calibration curve, but further data manipulation and calculation is needed to calculate either the weight average molecular weight or the number average molecular weight. The specification does not describe the calculation of the average molecular weight, which would have indicated to the person of skill in the art that the average molecular weight referred to is a peak molecular weight.

62. Further, according to the specification, Figure 1 displays the molecular weight distribution of three batches of copolymer-1. See the '808 Patent, col. 1, lines 57-59. The legend of both Figure 1 and Figure 2 indicates that the batches have "average molecular weights" of 7.7, 7.7, and 12.0 kDa. The peaks of the curves are close to those numbers, which would support the assumption that the numbers in the legend were peak molecular weights. A person of skill in the art would have understood that the molecular distribution curves in Figure 1 are transformed from SEC chromatograms, and that the

process of transferring the data from the chromatogram would likely cause the peak on each curve to shift slightly. Each curve in Figure 1 is identified with an average molecular weight. On the curves identified with an average molecular weight of 7.7 kDa, I measured the peak to be at 6.8 kDa[14]; on the curve identified with an average molecular weight of 12 kDa, I measured the peak to be at 11 kDa. A person of skill in the art would have understood that the peak positions on the curves are within a margin of error of the corresponding identified average molecular weights.

63. A person of skill in the art, knowing that there are other average molecular weights that are used to describe polymers, could also have considered the possibility that the term "average molecular weight" refers to number average molecular weight M_n or weight average molecular weight M_w. However, a person of skill in the art would have understood that, on a molecular weight distribution curve, M_n typically is smaller than M_p. Therefore, if the "average molecular weights" referred to in Figure 1 were M_n, the person of skill would have expected the peak on the curve to have a higher value than 7.7 (or be shifted to the right of 7.7), not a lower value. For this reason, a person of skill in the art would not have interpreted the term "average molecular weight" to mean M_n.

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[14] I note that the minor tick between 0 and 10000 on the x-axis of Figure 1 is not at the halfway point and therefore does not correspond to a molecular weight of 5000. Accordingly, the peak position on the x-axis was determined based on the major tick at 10000.

64. Based on Figure 1, a person of skill in the art would also have been able to tell that the corresponding M_w for both the 7.7 and 12.0 kDa curves would be significantly larger than the average molecular weights stated in the legend, and therefore would not have interpreted the term "average molecular weight" to mean M_w. Although, during the prosecution of the '847 patent (which does not include any claim that recites "average molecular weight"), the applicants stated that "kilodalton units implies a weight average molecular weight," (see the '847 patent prosecution history, 6/26/2002 Amendment (attached as Exhibit J), page 3 [TEV000304498]), a person of skill in the art would have understood that to be a misstatement because kilodalton is the unit for any measurement of molecular weight[15], not just M_w, and the person of skill would have recognized that M_w would very likely be greater than stated in the Figures based on the information provided in the curves.

65. During the prosecution of the '539 patent, in response to the Patent Examiner's rejection of the term "average molecular weight" based on indefiniteness, the applicants explained that "average molecular weight" refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1. See Exhibit G, the '539 patent prosecution history, 12/1/2004 Amendment, page10 [TEV000304803]. Based on the information provided in the patents-in-suit, a person of skill in the art would have accepted this interpretation as being accurate.

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[15] See footnote 2 above.

66. For the reasons stated above, the term "average molecular weight" would have been understood by a person of skill in the art to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column."

K. Copolymer species ... non-uniform with respect to molecular weight and sequence

67. In my opinion, the term "non-uniform" would have been understood by a person of skill in the art to have an ordinary meaning of "not always the same" or "varying."[16] In the context of claim 1 of the '098 patent, the "copolymer species" refers to the species in a mixture of copolymers of alanine, glutamic acid, lysine, and tyrosine. As such, a person of skill in the art would have understood the term "copolymer species ... non-uniform with respect to molecular weight and sequence" to mean "polypeptides composed of alanine, glutamic acid, lysine, and tyrosine, having different molecular weights and amino acid sequences."

L. Mixture of polypeptides ... non-uniform with respect to molecular weight and sequence

68. In my opinion, the term "non-uniform" would have been understood by a person of skill in the art

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[16] The word "uniform" is defined as "having always the same form, manner, or degree: not varying or variable." See Webster's Ninth New Collegiate Dictionary, 1988, p. 1290 (attached as Exhibit K).

to have an ordinary meaning of "not always the same" or "varying."[17] In the context of claim 1 of the '539 patent, the "mixture of polypeptides" refers to the polypeptides composed of glutamic acid, lysine, alanine, and tyrosine. As such, a person of skill in the art would have understood the term "mixture of polypeptides ... non-uniform with respect to molecular weight and sequence" to mean "mixture of polypeptides having different molecular weights and amino acid sequences."

M. Predetermined

69. In my opinion, the term "predetermined" would have been understood by a person of skill in the art to have an ordinary meaning of "determined beforehand." See Webster's Ninth New Collegiate Dictionary, 1988, p. 926 (attached as Exhibit L).

N. Test reaction

70. In the context of the patents-in-suit, the test reaction is conducted for a specific purpose, namely to study the effects of varying reaction conditions, e.g., time and temperature, on the results of the reaction, e.g., the molecular weight of the product. Example 4 of the specification states that "a test reaction is performed on every batch at different time periods for example, from 10-50 hours." See the '808 patent, col. 4, lines 65-67. Example 4 further states that "[t]he results concerning the molecular weight of these small scale reactions are calculated and a curve of molecular weight against time is

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[17] See footnote 16 above.

drawn. The time needed ... is calculated from the curve and performed on larger scale reaction." See the '808 patent, col. 5, lines 1-5. However, Example 4 does not state or indicate the small scale reaction is performed on the same batch of protected copolymer-1 used in the "larger scale reaction." As such, a person of skill in the art would have understood that the test reactions could be performed on a separate batch and there may not necessarily be a corresponding "large scale" reaction for every test reaction. Indeed, a person of skill in the art would have understood that the knowledge obtained from any test reaction could be applied to other reactions performed under similar conditions later. In my opinion, a person of skill in the art would have understood the term "test reaction" to mean "reaction carried out to determine results of varying reaction conditions."

O. Over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa

71. As stated above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Therefore, in my opinion, the term "over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" would have been understood by a person of skill in the art to have an ordinary meaning of "over 75% of molecules in a sample, as compared to the total number of molecules in the sample, have molecular weights

greater than about 2 kilodaltons and less than about 20 kilodaltons."

P. Over 75% of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of 2 kDa to 20 kDa

72. As stated above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Therefore, in my opinion, the term "over 75% of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of 2 kDa to 20 kDa" would have been understood by a person of skill in the art to have an ordinary meaning of "over 75% of copolymer molecules in the mixture, as compared to the total number of copolymer molecules in the mixture, have molecular weights greater than 2 kilodaltons and less than 20 kilodaltons."

Q. Over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons

73. In my opinion, the term "over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "over 75% of molecules making up copolymer-1 in the fraction have molecular weights greater than about 2 kilodaltons and less than about 20 kilodaltons.

R. Over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons

74. As stated above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Therefore, in my opinion, the term "over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "over 75% of polypeptides in the mixture, as compared to the total number of polypeptides in the mixture, have molecular weights greater than about 2 kilodalton and less than about 20 kilodaltons."

S. Less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons

75. In my opinion, the term "less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 5% of the molecules making up copolymer-1 have molecular weights greater than 40 kilodaltons."

T. Less than 5% of the copolymers have a molecular weight above 40 kDa

76. In my opinion, the term "less than 5% of the copolymers have a molecular weight above 40 kDa" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 5% of the copolymer molecules have molecular weights greater than 40 kilodaltons."

U. Less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons

77. As stated above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture. Therefore, in my opinion, the term "less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 5% of the total number of polypeptides in the mixture have molecular weights greater than 40 kilodaltons."

V. Less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons

78. As stated above, molar fraction is equivalent to the number of molecules of a particular component in the mixture divided by the total number of molecules of all components in the mixture.

Therefore, in my opinion, the term "less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 2.5% of the total number of polypeptides in the mixture have molecular weights greater than 40 kilodaltons."

W. Less than 2.5% of the copolymers in the mixture have a molecular weight above 40 kDa

79. In my opinion, the term "less than 2.5% of the copolymers in the mixture have a molecular weight above 40 kDa" would have been understood by a person of skill in the art to have an ordinary meaning of "less than 2.5% of the copolymer molecules have molecular weights greater than 40 kilodaltons."

X. The molecular weight range claim terms

80. In my opinion, a person of skill in the art would have understood the term "about" to have its ordinary meaning of approximately, and would have understood the actual numbers and unit of kilodalton to have their customary meanings. Specifically, a person of skill in the art would have understood the term "6.25 to 8.4 kilodaltons" to mean "6.25 to 8.4 kilodaltons," the term "about 4 to about 8.6 kilodaltons" to mean "approximately 4 to approximately 8.6 kilodaltons," the term "4 to 8.6 kDa" to mean "4 to 8.6 kilodaltons," the term "about 5 to about 9 kilodaltons" to mean "approximately 5 to

approximately 9 kilodaltons," the term "about 5 to 9 kilodaltons" to mean " approximately 5 to 9 kilodaltons", the term "about 4 to about 9 kilodaltons" to mean "approximately 4 to approximately 9 kilodaltons," the term " 7000 Da ± 2000 Da" to mean "5 to 9 kilodaltons," the term "4 to 8 kDa" to mean "4 to 8 kilodaltons," the term "7 to 8 kDa" to mean "7 to 8 kilodaltons," the term " 7.7 kDa" to mean "7.7 kilodaltons," the term "about 7.7 kDa" to mean "approximately 7.7 kilodaltons," and the term "greater than about 8.6 kilodaltons" to mean "more than approximately 8.6 kilodaltons."

I declare under penalty of perjury that the factual statements contained herein are known by me or believed by me to be correct.

Dated: October 6,2009

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Dr. Gregory A. Grant

[EXHIBITS A-L OMITTED]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., Plaintiffs, -against- SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC., Defendants.	Index No. 08 CV 7611 (BSJ) **DECLARATION OF FRANTISEK SVEC, PH.D. IN SUPPORT OF DEFENDANTS SANDOZ INC.'S AND MOMENTA PHARMACEUTICALS, INC.'S OPENING CLAIM CONSTRUCTION BRIEF**

I, Frantisek Svec, Ph.D. hereby declare as follows:

QUALIFICATIONS

1. I am the Facility Director at the E.O. Lawrence Berkeley National Laboratory in Berkeley, California. I am also a faculty member—currently a Visiting Scholar—at the University of California, Berkeley. A true and correct copy of my curriculum vitae is attached hereto as Exhibit 1. The following is a summary of my qualifications.

2. I earned a B.S. in chemistry from the Institute of Chemical Technology, Prague, Czech Republic in 1965. I also earned a Ph.D. in polymer chemistry from the Institute of Chemical Technology, Prague, Czech Republic in 1969.

3. In addition to my current appointments, other positions that I have held include: Assistant Professor, Institute of Chemical Technology, Prague, Czech Republic (1969¬1976); Visiting Scientist, University of Karlsruhe, Karlsruhe, Germany (1971-1972); Scientific Secretary and Technology Transfer Manager, Institute of Macromolecular Chemistry, Czech Academy of Sciences, Prague, Czech Republic (1976-1992); faculty, Cornell University, Ithaca, New York (1992-1996); and Visiting Professor of Analytical Chemistry, University of Innsbruck, Innsbruck, Austria (2003-2006). During my time at Cornell and the University of California, Berkeley, I generated synthetic polymers and determined their molecular weight parameters.

4. My main scientific interests include, but are not limited to: analytical and polymer chemistry; development of new separation media in various shapes and formats for different modes of separation; porous polymer monoliths; polymeric supports and catalysts; suspension, emulsion, and dispersion polymerization techniques; monodisperse beads, porous materials; chemical modification of polymers; and microfluidic and capillary systems.

5. I have authored or co-authored over 370 publications, including 56 book chapters and review articles as well as 3 books. A true and correct copy of my complete list of publications is attached hereto as **Exhibit 2**.

6. I am an inventor or co-inventor on 77 patents. A true and correct copy of my complete list of patents is attached hereto as **Exhibit 3**.

7. I am currently the Editor-in-Chief of the Journal of Separation Science. I also serve on the editorial boards of the following journals: *Journal of Chromatography A*, *Electrophoresis*, *Chinese Journal of Chromatography*, *Macromolecular Materials and Engineering*, *Chemical Letters (Prague)*, and the *Latin American Journal of Chromatography*.

8. I have been President of the California Separation Science Society since 2003. I am also a member of the American Chemical Society, the Czech Chemical Society, and the permanent steering committees of several international symposia on chromatography and related techniques.

9. I am the 2008 recipient of the American Chemical Society (ACS) Award in Chromatography, which recognizes outstanding contributions to the field of chromatography. I received this award for the design and development of monolithic columns based on rigid porous polymers and its major impact on modern chromatography. I am also the 2009 recipient of the Dal Nogare Award, one of the oldest and most prestigious awards given in chromatography, awarded on the basis of contributions to the fundamental understandings of the chromatographic process. Other awards that I have received include: the Czechoslovak Academy of Sciences Award (1986), the Czech National Prize (1988), the Journal of Chromatography Top Cited Article Award (2005), the M.J.E. Golay Award and Medal in Chromatography (2005), and the Eastern Analytical Symposium (EAS) Award for Achievements in Separation Science (2005). The Czechoslovak Academy of Sciences Award (1986), and the Czech National Prize (1988) were awarded for my research in polymer science.

10. I have been asked by counsel for Sandoz Inc. and Momenta Pharmaceuticals, Inc. to provide this declaration regarding the molecular weight limitations in U.S. Patents Nos. 6,620,847; 6,939,539; 6,054,430; 7,199,098; 5,800,808; 5,981,589, 6,342,476, 6,362,161, and 6,048,898 (collectively "the patents-in-suit" or "the patents").

11. I have reviewed the common specification of the patents-in-suit and each of the asserted claims. I have also reviewed U.S. Patent No. 3,849,550.

12. There are different fields of art that are relevant to the patents-in-suit. In my opinion, a person of ordinary skill in the art in the field of molecular weight determination of polymers as it relates to the patents-in-suit as of May 1994 would have been a person with a Ph.D. in polymer chemistry, with a minimum of three years of experience in chromatography, and specifically in size exclusion chromatography of polymers and their detection.

13. I consider myself to have been in 1994, and at all times thereafter continuing to the present to be, a person of at least ordinary skill in the art of chromatography and the molecular weight determination aspects of the patents-in-suit.

OPINIONS

14. It is my understanding that a patent claim is indefinite under the patent laws if one of ordinary skill in the relevant art would not understand the bounds of the patent claims when read in light of the patent specification. Applying that standard, it is my opinion that all claims in the patents-in-suit containing a "molecular weight" limitation are indefinite. The claims are insolubly ambiguous because the patents-in-suit do not specify the type of average molecular weight or the measurement techniques used to calculate the average molecular weight of the claimed low-molecular weight fractions of copolymer-1.

15. In the context of individual molecules, the term "molecular weight" refers to the sum of the

atomic weights of the elements making up a molecule. For example, the molecular weight of water (H2O) is calculated by adding the atomic weights of two hydrogen atoms (1.008 atomic mass unit ("amu") per atom) and one oxygen atom (15.999 amu per atom) for a total molecular weight of 18.015 amu.

16. Copolymer-1, however, is not an individual molecule. Rather, it is a copolymer. The copolymers at issue are a heterogeneous mixture of polypeptides having varying size and amino acid compositions. Unlike small molecules, polymer mixtures like copolymer-1 cannot be represented as a singular number that is the "sum of atomic weights of the atoms making up a molecule."

17. In the context of copolymer-1, any "molecular weight" limitation necessarily refers to a distribution of molecular weights or "average" molecular weights, not the weights of individual molecules, because copolymer-1 is composed of a mixture of many different sized molecules, which is referred to as a "polydisperse mixture."

18. When discussing the "molecular weight" of polymer mixtures, it is necessary to rely on the *average* molecular weight of the polymers in the mixture.

19. Scientists have developed different types of "averages" to describe any population, including a population of polymer molecules.

20. Two examples of averages are "number average" and "weight average," which provide different information and hence different numerical values for the same polydisperse population.

21. For example, a "half blueberry and half watermelon" fruit smoothie would be very different depending on whether the "half" refers to the *number* of watermelons and blueberries, or the *weight* of watermelons and blueberries. A "number average" fruit smoothie (one watermelon and one blueberry) would have much more watermelon than blueberry. On the other hand, a "weight average" fruit smoothie (equal weight watermelon to equal weight blueberry) would have the same weight of each fruit, but require many blueberries and much less than one watermelon to make the smoothie. In this example with watermelons and blueberries, the mixtures differ significantly in size and content depending on whether a "number average" or "weight average" is used.

22. The same principles hold true for polymer mixtures.

23. While number average and weight average are two of the more commonly used average molecular weights for describing polymer mixtures, they are not the only averages that can be used. The different averages all provide different information.

24. It is true that no single average molecular weight, whether it is the number average, the weight average, or some other average, is fully satisfactory for the characterization of a polymer mixture.

25. While "weight" seems like a simple physical property, it is the variety of different-sized molecules in a polymer mixture like copolymer-1 that makes "molecular weight" a complicated question for such mixtures.

26. Although the terms "molecular weight" and "average molecular weight" were included in the claims, the asserted patents never identify which "average" is used to describe the claimed molecular weights.

27. Moreover, because molecular weights of copolymers vary depending upon the measurement technique and the conditions used, the claims are further ambiguous.

28. It is my understanding that the applicants of the patents-in-suit told the Patent and Trademark Office that "[t]he molecular weight profile represents the percentage of copolymer-1 or trifluoroacetyl copolymer-1 having a molecular weight above a given amount." That statement provides no information regarding the particular type of average molecular weight measurement.

29. It is also my understanding that the applicants stated that molecular weight "may be determined using any method known to those in the art." That statement likewise provides no information regarding the particular type of average molecular weight measurement to be used.

30. It is my understanding that the patent applicants also stated that "one of ordinary skill in

the art could understand that kilodalton units implies a weight average molecular weight."

31. The "dalton" is one basic unit of molecular weight used in the patents. A kilodalton is 1000 daltons.

32. A dalton is defined as 1/12 of the mass of a single atom of the carbon isotope ^{12}C.

33. The applicants' statement that "one of ordinary skill in the art could understand that kilodalton units implies a weight average molecular weight" is not true because each type of "average molecular weight" can use the dalton.

34. When used as a unit for a polymer's average molecular weight, the "dalton" only has meaning if the type of average is specified and if the average is compared to a defined standard or calibration curve.

35. It is my understanding that the patent applicants also stated that "[o]ne of ordinary skill in the art, upon reviewing the specification, would understand that 'average molecular weight' refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1, which is the '% of the total mass' versus 'molecular weight.'"

36. "Peak average" refers to the molecular weight at the apex (or peak) of a molecular weight distribution curve. While "peak molecular weight" is not a true mathematical "average," it is commonly referred to as "peak average."

37. The applicants' statement that "[o]ne of ordinary skill in the art, upon reviewing the specification, would understand that 'average molecular weight' refers to the molecular weight at the peak of the molecular weight distribution curve ." is incorrect because the size exclusion chromatography technique in the specification can give at least peak average, number average, and weight average "molecular weights."

38. There is nothing in the specifications of the patents-in-suit that would require one of ordinary skill to understand that "peak average" is used.

39. A person of ordinary skill in the art could not determine that one type of average molecular weight is used in the patents-in-suit.

I declare under the penalty of perjury that the foregoing is true and correct and that this Declaration was signed this 7th day of October, 2009 at Berkeley, California

By:_____
Frantisek Svec, Ph.D.
Declarant

[EXHIBITS 1-3 OMITTED]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., Plaintiffs, -against- SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC., Defendants.	Index No. 08 CV 7611 (BSJ)

DECLARATION OF JIM ANDERSON, PH.D. IN SUPPORT OF DEFENDANTS SANDOZ INC.'S AND MOMENTA PHARMACEUTICALS, INC.'S OPPOSITION CLAIM CONSTRUCTION BRIEF

I, Jim Anderson, submit the following declaration in support of Sandoz Inc.'s and Momenta Pharmaceutical's Inc.'s brief in opposition to Plaintiffs' ("Teva's) claim construction positions.

1. I am the Vice President for Analytical and Drug Product Development at Momenta Pharmaceuticals, Inc. ("Momenta").

2. Momenta is a biotechnology company with a product pipeline of generic and novel drugs. The company focuses on building a thorough understanding of the structure-process-activity of known drugs to develop generic versions of marketed products. Momenta, through a team of scientists, applies its core analytical and proprietary technology to thoroughly characterize the structure of marketed products. By defining the chemical composition of multiple batches of a marketed product, we are able to develop an "equivalence window," which captures the inherent variability of the branded company's manufacturing process. Using this information, we then design and control our manufacturing process to manufacture reproducibly an equivalent version of the marketed product. Our goal is to obtain FDA approval and to commercialize generic or follow-on versions of known drug products, thereby providing high quality, safe and affordable medicines to patients in need.

3. I joined Momenta in March 2007. Before joining Momenta, I was a Director at Bristol-Myers Squibb Medical Imaging for seven years. Before that, I was a Director and Research Scientist at DuPont Pharmaceuticals for seven years. Before joining

DuPont, I was an Assistant Professor at Boston College and a Visiting Assistant Professor at the University of Houston. I obtained my Ph.D. from the University of Michigan in 1985.

4. Since joining Momenta, I have continuously been involved in Momenta's M356 project. M356 is a technology-enabled generic version of Teva's Copaxone® (glatiramer acetate injection). M356 is a joint collaboration with Sandoz.

5. My responsibilities on the M356 project included preparing significant portions of the December 2007 Abbreviated New Drug Application ("Sandoz's ANDA") at issue in this case. I was personally involved in drafting, editing, or developing the background for the sections regarding the determinations of molecular weight.

6. At the time the ANDA was filed, I was Momenta's CMC leader for the M356 project. "CMC" refers to the "Chemistry, Manufacturing and Controls" section of submissions to the FDA seeking approval to market a drug.

7. Determining the average molecular weight for the proposed product described in Sandoz's ANDA is a major aspect of Momenta's M356 project. I am familiar with the substantial scientific effort that went into finalizing the techniques for measuring the molecular weights described in Sandoz's ANDA.

8. I am familiar with the "Konfino patents," which I understand are the patents asserted in this litigation (the "Konfino patents").

9. It is my understanding that the parties in this litigation dispute whether the use of the terms "molecular weight" and "average molecular weight" in the Konfino patents are sufficiently "definite" for scientists skilled in the art to understand whether a generic applicant's products and methods fall within or outside of the patent claim scope.

10. It is my understanding that Teva has cited statements made in Sandoz's ANDA regarding "average molecular weight" to support its argument that the use of the terms "average molecular weight" and "molecular weight" in the Konfino patents are sufficiently "definite," as that term is used in patent law. Specifically, it is my understanding that Teva cited a statement i Sandoz's ANDA, which notes that the Copaxone® product label lists an average molecular weight of glatiramer acetate as 5,000 to 9,000 Daltons. I am familiar with both the Copaxone product label and statement in the Sandoz ANDA cited by Teva.

11. The conclusion for the M356 project that the molecular weight description in the Copaxone product label references "peak molecular weight" resulted from years of scientific research and studying of public disclosures by Teva not found in the Konfino patents. This included extensive molecular weight testing of commercially obtained Copaxone product.

I declare under the penalty of perjury that the foregoing is true and correct, and that this

Declaration was signed this 3rd day of November 2009 at San Francisco, California.

By: _____
Jim Anderson

[Exhibit 16 to the Declaration of Brian M. Kramer]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC.,	)	
and	)	
YEDA RESEARCH AND DEVELOPMENT CO., LTD.,	)	
Plaintiffs,	)	
vs.	)	Civil Action No.
SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG	)	08 CV 7611 (BSJ)(AJP) ECF Case
and	)	
MOMENTA PHARMACEUTICALS, INC.,	)	
Defendants.	)	

VIDEOTAPED DEPOSITION OF GREGORY A. GRANT, PH.D.

TAKEN ON BEHALF OF THE DEFENDANTS

[16]

answered.

A. I wouldn't say that it it's not actually an average because it depends upon how the viewer is considering it.

Q. (By Mr. Aannestad) What way does it depend on how the viewer is considering it?

A. Whether or not the viewer is considering only the single point at the apex of the curve, or whether the viewer is also considering points on either side of that apex.

Q. How does considering points on either side of the apex make that an average?

A. Because once you consider more than one point and you come up with a single number, you are in effect averaging.

Q. Okay. But if you are looking at peak molecular weight only –

A. Uh-huh.

Q. -- is that an average?

A. I would say that in the truest form it probably is not.

Q. So in truth, peak molecular weight is not an average molecular weight?

MS. HOLLAND: Objection to form, [17] mischaracterizes the testimony.

A. It is often referred to as an average molecular weight in the literature.

Q. (By Mr. Aannestad) But in truth, it is not, is it?

MS. HOLLAND: Objection to form.

A. If one is using the apex of the curve to express the peak average molecular weight, in truth it is not a real average.

Q. (By Mr. Aannestad) Do you refer to peak molecular weight as an average in your literature?

A. I do not recall whether I've done so.

Q. Do you ever recall having done that?

A. I do not recall. I have a great deal of literature going over many years.

Q. About how many papers have you published?

A. Over a hundred. Again, I don't recall the exact number, but it's -- if you consider invited articles, it's in the vicinity of 120.

Q. How about book chapters?

A. I've edited two books and I have written chapters in each of them.

Q. And lectures, do you give lectures?

A. I have given lectures in the past. I do

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attached. So in that sense it's not an exact copy.

MR. AANNESTAD: Which I already noted, but thanks.

A. With the exception of the exhibits and based upon my quick perusal, it appears to be an accurate copy.

Q. (By Mr. Aannestad) What is your current position?

A. I am professor of biochemistry in medicine and of molecular -- or developmental biology, excuse me, at the Washington University School of Medicine. And I am director of the protein and nucleic acid chemistry laboratories at the same institution.

Q. In paragraph two of your declaration, it states in the last sentence that your research is focused primarily on the investigation of regulatory processes of proteins; is that correct?

A. That is essentially correct, yes.

Q. Okay. And what do you mean by that?

A. I study how proteins are regulated.

Q. Is the focus of that work chromatography?

MS. HOLLAND: Objection to form.

A. Again, if you mean by focus, if the work is directed at developing chromato – chromatography [21] techniques, no. It is not. But it uses chromatography techniques regularly.

Q. (By Mr. Aannestad) So you use chromatography techniques, but you do not develop them?

A. That's correct.

Q. The next paragraph states that you and your staff in your role directing this protein and nucleic acid chemistry laboratory provide sophisticated analytical and synthetic research capabilities; is that right?

A. I believe it to be.

Q. What do you mean by "sophisticated analytical capabilities"?

A. Well, sophisticated depends on your definition. I would consider it to mean that it is complex and detailed, and something that perhaps not everyone can perform without training.

Q. What type of -- well, let me step back.

Are those calculations? What do you mean by that?

A. No. They are -- they are methods. They are methods of analysis and methods of synthesis.

Q. Do you do analysis of data?

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[24]

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Q. Do you do calculations in your work at PNACL of percent mass of the polymer mixture?

A. I may have in the past. Again, I I don't do this routinely unless I'm asked to do it.

Q. So that's not work that routinely comes up in your role directing the PNACL?

A. That is correct.

Q. Paragraph four where you say, "I have used this technique" referring to SEC, "to measure the

molecular weights of proteins." What do you mean by you have used the technique? How many times?

A. I've used it a large number of times and I cannot tell you an exact number.

Q. In your analytical work at the PNACL, do you ever do calculations of area under the curve?

A. We have software that is capable of doing that.

Q. Are you capable of doing that yourself by hand?

A. I think that I am, but I do not remember the last time that I did it.

Q. You're familiar with that type of calculation, though?

A. Yes.

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[39]

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Q. Did you do in making this statement about the prior art copolymer-1 having a peak molecular weight of 23,000, did you do any analysis of the '550 patent to make that statement?

A. I don't recall that I did.

Q. The sentence in this paragraph sixteen that states, "In addition, the patents describe methods of making copolymer-1 of lower molecular weight," you're not referring to the '550 patent there, right? You're referring to the '808 and the patents-in-suit, correct?

A. I believe that I am, to my recollection.

Q. Okay. What methods are described?

A. Could you be more clear as to what you mean by "methods"?

Q. Well, what do you mean when you say "the patents described methods of making copolymer-1 of lower molecular weight"? And if you need a copy of the '808 patent, I have that. I'm handing you what's been previously marked Exhibit DDX 28.

A. The patent that I have in front of me describes the method by which copolymer-1 of certain molecular weights is made.

Q. Maybe we should break it down. You state [40] here examples one, three, and four, correct?

A. Correct.

Q. What does example one teach?

MS. HOLLAND: Objection to form.

A. Example one teaches how a batch or batches of copolymer-1 was fractionated.

(Court reporter interruption.)

A. Fractionated.

Q. (By Mr. Aannestad) So does that mean a larger molecular weight batch was made and then a fraction having smaller molecular weights was extracted from that?

MS. HOLLAND: Objection to form.

A. That appears to be the case.

Q. (By Mr. Aannestad) What does example three teach?

A. Example three teaches how the copolymer-1 was produced from N-carboxyanhydrides of various amino acids and how certain protecting groups were removed from the product.

Q. Does it teach making low molecular weight copolymer-1?

MS. HOLLAND: Objection to form.

A. It doesn't mention low molecular weight [41] that I can see.

Q. (By Mr. Aannestad) What does example four teach?

A. Example four teaches, again, the method by which copolymer-1 is produced from N-carboxyanhydrides of certain amino acids. It teaches how the polymerization process is initiated. It teaches how that process was handled. It teaches how certain protecting groups were removed.

Q. Does it teach making low molecular weight copolymer-1?

A. I do not believe it mentions that.

MS. HOLLAND: Ob -- objection to form.

Q. (By Mr. Aannestad) If you turn the page to column five, does that continue example four?

A. It appears to.

Q. Does any of that text teach making low molecular weight copolymer-1?

MS. HOLLAND: Objection to form.

A. It does not specifically refer to low molecular weight, but it does refer to a molecular weight.

Q. (By Mr. Aannestad) Do any of these examples teach directly making a low molecular weight [42] copolymer-1 as opposed to making the larger molecular weight batch and extracting or reducing down to low molecular weight?

MS. HOLLAND: Objection to form. Please take as long as you need to read this.

A. As far as I can see, it teaches making a copolymer-1 of a specific molecular weight.

Q. (By Mr. Aannestad) Well, let's -- let's look at in example four, look at column four, line 59. Do you see it starts "Protected copolymer-1"?

A. Yes.

Q. Can you please read that sentence for the record?

A. "Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue" –

(Court reporter interruption.)

A. -- "5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides."

Q. (By Mr. Aannestad) What is meant by the "cleaves the polymer to smaller polypeptides"?

A. It means that smaller polypeptides were produced and implies they were produced from larger [43] polypeptides.

Q. Okay. So in example two, a fraction of smaller peptides is extracted, correct?

MS. HOLLAND: Objection to form.

Q. (By Mr. Aannestad) Oh, I'm sorry. Okay. Let -- let me re-ask this.

In example one a fraction of smaller copolymer-1 is extracted from the batch of larger copolymer-1, correct?

A. I'd like to read it first. As I read example one, it states that a fraction having an average molecular weight of seven to eight kilodaltons was isolated. It doesn't explicitly state that any other sizes were there.

Q. Well, what's your understanding of that fraction being isolated?

A. Well, I said in my declaration that I consider fraction to mean the portion of a whole. So if it says a fraction of average molecular weight of seven to eight kilodaltons was isolated, according to that definition, it would mean that the seven to eight kilodalton fraction was a portion.

Q. A portion of copolymer-1 having that particular molecular weight?

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A. I don't know that I would prefer to speculate.

Q. Okay. Do you know if example one describes the batches in figures one and two?

A. I don't know it.

Q. In paragraph 21 you have a description of your opinion of what a person of ordinary skill in the art

would have in terms of degree and experience; is that correct?

A. Paragraph 21 deals with that.

Q. Okay. Are you a person of ordinary skill in the art of these patents?

A. I believe that I am.

Q. Were you a person of ordinary skill in the art of these patents in 1994?

A. You're referring to the art that is contained in the patents-in-suit?

Q. Yes, the field of the patents.

A. Insofar as it relates to my declaration, I believe that I was.

Q. At the end of the paragraph 21 you mention toxicology; is that correct?

A. That is correct.

Q. What do you mean by that?

[53]

A. I believe it to mean the study of substances that are toxic.

Q. Why would a person of ordinary skill in the art consult with a person with knowledge and experience in toxicology?

A. If the patents refer to toxicology or the toxicity of a substance, a person may want to refer to someone who is trained in that area.

Q. Trained in toxicology for humans?

A. It's not specified.

Q. Do you believe it would be limited to someone who is trained in toxicology for animals?

MS. HOLLAND: Objection to form, outside the scope of his declaration.

A. I don't believe it would be limited.

Q. (By Mr. Aannestad) Looking at footnote two on that page, what do you mean by "relative atomic and molecular weights are dimensionless quantities"?

A. What part of that question do you want me to answer, because I can -- I see that there are two parts?

Q. Okay. Well, what's the first part?

A. Relative atomic and molecular weights.

Q. Please discuss that.

[54]

MS. HOLLAND: Objection to form. Is that a question?

Q. (By Mr. Aannestad) Describe what you mean.

A. My ordinary use of the term "relative" means when one thing is compared to another.

Q. Are average molecular weights of polymers like copolymer-1 compared to a standard?

A. That's not what this footnote refers to.

Q. But is that true?

A. Could you repeat the question?

Q. Are the average molecular weights of polymers like copolymer-1 generated by comparison to a standard?

A. I believe that the numbers are derived by comparison to standards.

Q. Are they also dimensionless quantities?

A. Molecular weights technically are dimensionless quantities.

Q. Why is that?

A. Because that's the science.

Q. What do you mean "that's science"?

A. I mean, that's -- that's what I have been taught and that is what is in the literature. And that is what other scientists who have gone before me [55] have determined.

Q. Is it because they're relative it doesn't really matter what the dimension is; it's a relative number?

A. It's because you're talking about a number and not about a mass.

Q. What's the second part of that statement?

MS. HOLLAND: Objection to form.

A. Well, the second -- what I was referring to after "relative" was the statement of dimensionless.

Q. (By Mr. Aannestad) Okay. Please discuss -- describe that for me.

A. I believe we've already discussed that.

Q. Please turn to paragraph 26 of your declaration. Do you see the first sentence there referring to molar fraction?

A. Yes, I do.

Q. What are the units of a molar fraction?

A. Molar fraction does not have a unit because it is a relative quantity.

Q. Please turn a number of pages to paragraph 34. It's on page fourteen. What do you mean by the phrase "a specific kind of polymer [sic]" in the first sentence of paragraph 34?

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[61]

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A. May I look at the paper?

Q. We'll have to do that after the break. You don't recall from your -- preparing your declaration?

A. I would like to verify. Anything I would say now -

MS. HOLLAND: If you need to verify, then that's fine.

MR. AANNESTAD: Well, we're running out of tape, so why don't we take a break?

VIDEOGRAPHER: We're going off the record at 10:11 a.m.

(WHEREIN, a recess was taken.)

VIDEOGRAPHER: We're back on the record on tape two at 10:28 a.m.

Q. (By Mr. Aannestad) Dr. Grant, does peak molecular weight describe the weight of the most species in a mix -- mixture?

MS. HOLLAND: Objection to form.

A. Describe the weight of most species?

Q. (By Mr. Aannestad) Of the most -- of the most species, the species there is the most of?

A. The peak molecular weight is determined at the apex of the peak. And there is more material there than in any other part of the peak.

[62]

Q. Does that mean that is the point where you have the most of a single species?

A. Not necessarily.

Q. When would that not be the case?

A. Could not be the case at any time. Just by looking at a peak you have no way of telling whether there's one or more species there.

Q. In paragraph 36 of your declaration at the second sentence you state, "The most precise way of describing the molecular weight of such a polymer is a complete molecular weight distribution, i.e., knowledge of the mole or weight fraction of each species." Do you see that?

A: I do.

Q. Is that possible for copolymer-1?

MS. HOLLAND: Objection to form.

A. I think it would be very difficult to do as a person skilled in the art. I think that it probably would take a very great effort to do it, and I'm not sure that it would be possible.

Q. (By Mr. Aannestad) Looking at the second part of that, the knowledge of -- of the mole or weight fraction of each species, is that -- is the measurement

of each fraction also an average molecular [63] weight?

A. If each fraction contains more than one species.

Q. And a fraction of copolymer-1 would contain more than one species, correct?

A. It could.

Q. Do you have any basis to believe that it would not?

A. It depends to how highly resolved the fractions are.

Q. In your opinion, is it possible to resolve a fraction of copolymer-1 that contains only one species?

A. It may be, but I wouldn't know unless I actually tried to do it.

Q. But if there's more than one species in that fraction, then that is a measurement of an average, correct?

A. If there is more than one species in the fraction and you come up with a single number to describe it, it is an average.

Q. Is it possible there would be species in that fraction that are -- I'll ask that later.

Looking at paragraph 39, do you see the [64] statement that "The values for Mn and Mw can be further calculated using the size exclusion chromatography data"?

A. I do.

Q. How is that done?

A. Which one?

Q. Let's start with Mn.

A. The size exclusion chromatography data relates the material as a measurement of the quantity versus the amount of time or the elution volume it took to come from the column.

Using a calibration curve, each fraction along the chromatogram can have a molecular weight determined for it, and you can produce a relative estimation of the amount of material at each point of the determination. In using that information, you can use an equation to determine Mn and come up with a number.

Q. Mn refers to number average, correct?

A. That is correct.

Q. Is that calculation done with software typically?

A. It can be, but doesn't have to be.

Q. Is it difficult to do that calculation?

[65]

MS. HOLLAND: Objection to form.

A. It's a matter of opinion. I do not believe it's difficult generally.

Q. (By Mr. Aannestad) Is it difficult to do the calculation of Mw, i.e., weight average molecular weight?

MS. HOLLAND: Objection to form.

A. It involves additional terms in the equation, but generally I do not consider it difficult.

Q. (By Mr. Aannestad) Do you consider it difficult in the context of copolymer-1?

MS. HOLLAND: Objection to form.

A. It depends to what extent you want to analyze it.

Q. (By Mr. Aannestad) But is there anything about copolymer-1 that -- that makes your opinion any different that it's generally not difficult?

A. I think that the values can be calculated for copolymer-1 without a great deal of difficulty.

Q. Look at footnote eleven of your declaration under page eighteen. What do you mean when you say, "For practical purposes, the molecules within each fraction are treated as if they have the same size"?

[66]

A. Well, as a matter of practicality you assume that once you have fractionated you do not have to do additional fractionation to arrive at a size.

Q. The fraction may well have molecules of different sizes, correct?

A. It may.

Q. Looking at page nineteen, please. You have a curve here. You see that?

A. Yes.

Q. Is that a Gaussian distribution?

A. I don't know.

Q. What is a Gaussian distribution?

A. Gaussian distribution is a distribution where there is equal area on both sides of the midpoint of a curve in a symmetrical manner.

Q. Does copolymer-1 have a Gaussian distribution?

A. If you just say copolymer-1, I mean, Gaussian distribution doesn't apply to copolymer-1 unless you produce a peak.

Q. Are you aware of any data showing batches of copolymer-1 that have Gaussian distribution?

MS. HOLLAND: Objection to form.

A. I do not recall that I have seen such.

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Q. (By Mr. Aannestad) What do you mean when you say doesn't -- Gaussian distribution doesn't apply to copolymer-1 unless you produce a peak?

(Court reporter interruption.)

Q. (By Mr. Aannestad) Gaussian distribution doesn't apply to copolymer-1 unless you produce a peak?

A. A Gaussian distribution applies to a curve. Copolymer-1 is not a curve.

Q. Okay. I see. So if you -- well, I think we've -- we've covered that.

Can you look at paragraph 42, please? Can you please read the second sentence for the record?

A. "An easier and more common method, however, is to correlate the elution volume or

retention time on the chromatogram to molecular weight through standards that have known molecular weights."

Q. Do you know what the molecular weights are of the standards used in the patents for the SEC?

A. No, I don't. They were not mentioned in the patents.

Q. Turn the page to page twenty, please. You have a polymer distribution curve there, correct?

A. Correct.

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MS. HOLLAND: Objection to form.

A. Whose definition of likely?

Q. (By Mr. Aannestad) Your definition of likely.

A. I would say it's in the realm of possibility. It probably would not be likely.

Q. Looking at paragraph 58, you state that "The ordinary meaning of the term 'range' is 'a set of values between an upper boundary and a lower boundary.'" Do you see that?

A. I see it.

Q. And then you say in your opinion, "the term 'molecular weight range' would have been understood by a person of skill in the art to mean 'a set of molecular weights between an upper boundary and a lower boundary.'" What do you mean by that?

A. By what?

Q. A set of molecular weights between an upper boundary and lower boundary?

A. You're referring to the word "set" specifically?

Q. I'm referring to that clause.

A. Okay. I mean a set of molecular weights between an upper boundary and a lower boundary.

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Q. How is that measured?

A. It is measured by a suitable method to determine molecular weight.

Q. So for co copolymer-1, would that be a measurement of the average molecular weight?

MS. HOLLAND: Objection to form.

A. My opinion is that the aver -- as stated in my declaration, that the average molecular weight as it applies to the patents-in-suit refers to peak molecular weight.

Q. (By Mr. Aannestad) But does the molecular weight within a range refer to average molecular weight?

A. If you say that it's within a range between X and X, I believe that it would refer to average molecular weight. Average molecular is one way to refer to it. When you say that a set occurs between boundaries, you're implying that there's more than one specific molecule.

Q. Please turn to paragraph 61 of your declaration. This describes your opinion to the Court regarding the meaning of average molecular weight, this section, correct, paragraphs 61 through 66?

A. Those paragraphs refer to average molecular [90] weight.

Q. Would you please read the first two sentences of paragraph 61 for the record?

A. "Example 1 of the specification states that the molecular weight distribution of copolymer-1 was determined on a calibrated gel filtration column, specifically a Superose 12 column, using a UVIKON spectrophotometer."

Q. Then there's a citation, correct, to that?

A. "See the '808 Patent, col. 3, lines 3-8."

Q. Please read the next sentence as well.

A. "As such, a person of skill in the art would have understood that the method of determining molecular weight distribution was size exclusion chromatography, and that a calibration curve was generated to correlate molecular weight with elution volume or retention time."

Q. So in your opinion, the inventors generated a calibration curve, correct?

A. Yes, I believe so.

Q. And that calibration curve is not described in the patents, correct?

A. I do not recall that it is.

Q. When you publish your papers on publish [91] papers that utilize SEC and calibration curves, do you prove the standards?

A. In general I do.

Q. Are you aware of any instances where you did not?

A. Sitting here right now, I am not aware. I'd have to review all the papers to be able to answer that question.

Q. Please read the sentence beginning "Peak molecular weight can be obtained directly."

A. "Peak molecular weight can be obtained directly from the chromatogram and the calibration curve, but further data manipulation and calculation is needed to calculate either the weight average molecular weight or the number average molecular weight."

Q. You rely on figures one and two of the patents for your opinion, correct?

A. Figures one and two are the only figures that are provided in the patents.

Q. And you rely on those, correct?

A. I -- for this statement and my opinion, I rely on my knowledge that that's the appropriate way to do it. Figures one and two are just examples of

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Q. Would you publish a paper using the term "average molecular weight" for a polymer, meaning peak molecular weight, without expressly telling the reader that?

A. Possibly. Because in my opinion it's implied.

Q. Why is it implied?

A. Because evidence for other usages are not provided.

Q. So in your opinion, is peak molecular weight the default meaning of average molecular weight if nothing else is stated?

A. In my opinion as far as the patents-in-suit are concerned, the meaning of average molecular weight is peak molecular weight.

Q. That's not my question. My question is: Is peak molecular weight the default meaning to a person of skill in the art of the term, quote, average molecular weight?

MS. HOLLAND: Objection to form, ambiguous.

A. As I said in the declaration, average molecular weight can refer to several different types of average molecular weight.

Q. (By Mr. Aannestad) Is any one of those [95] types a default meaning to a person of skill in the art?

A. I would not term it that way.

Q. Is there anything in the patents themselves that expressly state that average molecular weight means peak molecular weight?

A. I do not recall that there is, but I would have to go through the patents again to be able to answer that question completely. But I do know that it's expressed in the prosecution.

Q. Is peak molecular weight the ordinary meaning for average molecular weight?

A. As I stated before and in the declaration, there are several different meanings for average molecular weight. I do not know what you mean by ordinary.

Q. Looking at paragraph 62, do you see your statement, "The peaks of the curves are close to those numbers"?

A. I do.

Q. What do you mean by "close"?

A. I mean the common usage of the word "close," that they are similar. They're in the vicinity of.

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Q. Later on you state that a person of ordinary skill in the art -- let me correct that. "A person of skill in the art would have understood that the peak positions on the curves are within a margin of error of the corresponding identified average molecular weights." Do you see that?

A. I do.

Q. What margin of error are you referring to?

A. I don't believe I'm referring to a specific margin of error. I am referring to a margin of error.

Q. Any margin of error, is that what you're referring to?

A. Not any. A margin of error.

Q. What margin of error do you mean?

A. The margin of error that exists.

Q. And what -- what margin exists here?

A. Well, as stated in the declaration, 7.7 compared to 6.8. Twelve compared to eleven.

Q. And what is stated?

A. That's what's stated.

Q. What is stated about the margin of error?

A. There's no explicit statement that what the margin of error is, but it's my opinion that when you compare two values that are different, there is a [97] margin of error.

Q. Isn't any error a margin of error?

A. Any error can be, but it may not refer to this particular error.

Q. Well, if all you're saying is a margin of error, isn't fifty percent error a margin of error?

A. Fifty percent error –

MS. HOLLAND: Objection -- sorry, objection to form. You can answer.

A. Fifty percent error is a margin of error.

Q. (By Mr. Aannestad) Hundred percent error is a margin of error?

A. It is a margin of error.

Q. Two hundred percent error is a margin of error?

A. Sure.

Q. Two thousand percent error is a margin of error?

MS. HOLLAND: Gen -- I assume all these questions mean generally?

A. Yeah. A margin of error is a margin of error.

Q. (By Mr. Aannestad) Why didn't you state a particular margin of error here?

[98]

A. Didn't feel that it was necessary.

Q. Why not?

A. Because my opinion was that there was a margin of error.

Q. Did the lawyers suggest to you using a margin of error without specifying the particular margin of error?

A. I want to make it very clear that these are my opinions. These are not the lawyers' opinions.

Q. Okay.

A. I conferred with the lawyers and gave them my opinions. Somebody put words on a piece of paper. I reviewed it very, very carefully and agreed that they were my opinions.

Q. So you stand by all of these opinions?

A. I do.

Q. Would you use the phrase "a margin of error" to define your margin of error in a publication you're an author on?

A. I may very well use the expression that there is a margin of error. I may then or may not define what that margin of error is.

Q. You would publish a paper without stating what the margin of error is?

[99]

A. It depends the context in which it was used.

Q. In what context would you feel it's not necessary to state what margin of error you're using?

A. For instance, in the discussion section of a paper I could say that the data indicates that there is a margin of error. If that margin of error was listed someplace else in the paper, I don't have to restate it.

Q. Okay. If that margin of error is not listed somewhere else in the paper, would you need to state it?

A. If I wanted to make a point about it.

Q. Then yes?

A. I can say that there is a margin of error without needing to state what that margin of error is.

Q. But you need to state what that margin of error is somewhere, correct?

A. Depending upon what point I'm trying to make. If I'm trying to say that that margin of error is important for some particular point that I'm trying to make, then I suppose that I would want to state what it is. But it's not incorrect to say that there's a margin of error because, in fact, in [100] everything you do there is a margin of error.

Q. Is the margin of error here in paragraph 62 important?

A. That's a value judgment.

Q. In your opinion, is the margin of error in this paragraph 62 important for what you're trying to say?

A. In my

MS. HOLLAND: Object sorry, objection to form. Go ahead.

A. In my opinion, there is a margin of error, and by giving the numbers I have said what that margin of error is.

Q. (By Mr. Aannestad) What is the margin of error that you've stated?

A. The margin of error is not stated explicitly, but it can be deduced from the information given.

Q. Is there any objective standard to this margin of error?

A. Can you clarify what you mean by "objective standard"?

Q. Is there any objective basis on which you decided that the the differences stated in these [101] peaks are acceptable to you?

A. I did not state whether they were acceptable or not. I simply stated that they existed.

Q. Would you publish a paper using figure one?

MS. HOLLAND: Objection to form.

A. Figure one is not mine. Why would I publish it?

Q. (By Mr. Aannestad) Well, if -- if you -- would you publish a paper using figure one as it exists to describe that data without changing the figure at all?

MS. HOLLAND: Objection to form.

A. I mean, figure one is not my figure. I wouldn't publish it. I -- I mean, it's somebody else's property.

Q. (By Mr. Aannestad) Would -- would you publish a figure with the same errors as in figure one?

MS. HOLLAND: Objection to form. You can answer.

A. Possibly. Depends upon my reason for publishing it and the point that I was trying to make.

Q. (By Mr. Aannestad) What do you mean when you say in paragraph 62 "which would support the [102] assumption that the numbers in the legend were peak molecular weights"?

A. What line is that?

Q. It's in the third sentence of paragraph 62.

A. I do not see those words.

Q. "The peaks of the curves are close to the those numbers."

A. That's the --

Q. I was omitting the citation.

A. "The peaks of the curves are close to those numbers, which would support the assumption that the numbers in the legend were peak molecular weights."

Q. What do you mean that it's an assumption?

A. Well, the figure gives values for average molecular weights, and since calculations or descriptions of other types of molecular weights were

not given, and the only thing that was given was a peak, then my opinion is appropriate to assume that the legend refers to peak molecular weights.

Q. It's necessary to assume peak molecular weights because it's not expressly stated, correct?

A. The peak molecular weight is the only information that's provided.

Q. Does figure one expressly state that [103] average molecular weight means peak molecular weight?

A. No. It simply expresses average molecular weight.

Q. In your conclusion, that average molecular weight means peak molecular weight is based on your assumption, correct?

A. It's based on more than that.

Q. What else is it based on?

A. It's based on the fact that the -- as stated in my declaration, that the prosecution states that it is so.

Q. Other than the prosecution, is there anything in the patents that supports your opinion?

MS. HOLLAND: Objection, asked and answered. We've been talking about it for the last fifteen minutes.

A. I believe I have answered that.

Q. (By Mr. Aannestad) Other than the prosecution, is there anything else in the patents that supports your opinion?

A. Yes. A peak is provided on a scale with molecular weight.

Q. So based on what you have discussed in the patents, it's your assumption that average molecular [104] weight means peak molecular weight?

A. It is my opinion that average molecular weight refers to peak molecular weight.

Q. Based on an assumption?

A. Based upon my knowledge, based upon my experience.

Q. Based upon the lack of a discussion of calculating number average and weight average molecular weight, correct?

A. That, plus the fact that a peak is provided on molecular weight scale.

Q. Is there anything else in the patents themselves that you rely on for your opinion that a person of skill in the art would assume that average molecular weight means peak molecular weight?

A. Without reading the patents in their entirety, I do not recall that there is. But it is my opinion that that is correct.

Q. You state in this paragraph 62 "that the process of transferring the data from the chromatogram would likely cause the peak on each curve to shift slightly." Why is that?

A. Because any process that deals with manipulating data has an inherent error associated

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[113]

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estimate it.

Q. Why isn't it correct to do so?

A. Because it should be calculated from the original chromatogram.

Q. Why is that?

A. Because the original chromatogram holds the primary data.

Q. And is that more accurate?

A. I believe it would be. It's likely that it would be.

Q. Why are you willing to calculate the peak molecular weight as the average molecular weight from figure one if you're not willing to calculate the number average molecular weight?

A. I didn't say I'm not willing to.

MS. HOLLAND: Objection I'm sorry. Objection to form, mischaracterized the previous testimony.

Q. (By Mr. Aannestad) Why would you not?

A. I didn't say I wasn't willing to.

Q. Well, why would you not do that in your opinion?

A. Because I think you -- the correct way to do it is from the primary data.

[114]

Q. And would the correct way to calculate the peak be from the primary data?

A. I believe that is -- the average molecular weights which are provided in the legend are from the primary data, and that the differences that we have discussed come about from the transformation to this form.

Q. But you don't have any specific basis to know that there was a difference caused by the transformation?

A. I do not have the primary data.

Q. And you haven't asked for the primary data?

A. No, I have not.

(WHEREIN, Exhibit DDX 57 was marked for identification by the Court Reporter.)

Q. (By Mr. Aannestad) You've been handed Exhibit DDX 57. Can you please mark the apex of those curves?

A. I can mark what I believe to be the apex by visual inspection.

Q. Okay. I have a magnifying glass if that would be helpful.

A. I mean, I would point out that this is not what I was asked to do to base my opinion on.

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[116]

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handed in the same spot that you marked them in DDX 57?

A. [Witness indicates.]

Q. Can I see Exhibits DDX 57 and 58, please? Looking at the twelve kilodalton line on DDX 58, where does your marking of the peak measure on the X axis in molecular weight?

A. Well, first of all, there is not a twelve kilodalton line.

Q. Curve?

A. There is no designation of twelve kilodaltons there.

Q. Okay.

A. So I would have to estimate it visually.

Q. Is there a curve that corresponds to --

A. Are you referring to the twelve average molecular weight curve?

Q. Correct. In your opinion?

A. Okay. And the question –

Q. Yeah, that curve.

A. The question is?

Q. Yeah, where is the apex of that curve as marked by you on DDX 58?

A. It's approximately at 10,000.

[117]

Q. Is it slightly below 10,000?

A. Could be. It's very close.

Q. Does that change your opinion regarding the peak being at 11,000?

A. No, because I've done this by hand and visual inspection twice. There is inherent error in it.

Q. There's an even greater margin of error than previously?

A. Perhaps. But if I do it again there might be less.

MR. AANNESTAD: I think we need to change tapes.

VIDEOGRAPHER: We're going off the record at 11:47 a.m.

(WHEREIN, a recess was taken.)

VIDEOGRAPHER: We're back on the record on tape three at 12:03 p.m.

Q. (By Mr. Aannestad) Dr. Grant, looking at Exhibit DDX 58, where does your mark on the curve corresponding to the 7.7 molecular weight fall in terms of the X axis?

A. Well, I would have to estimate it based on the fact that that tick does not appear to be [118] accurate. But I would estimate -- without a ruler, it's difficult to appreciate that.

Q. Here's a ruler.

A. I estimate it's approximately seven.

Q. Can you do an area under the curve calculation for figure one?

A. Now?

Q. Yeah. Do you know how?

A. No, I do not.

Q. Can't do that sitting here?

A. No. That involves integration of that curve.

Q. Could you do an estimation of the area under the curve?

A. Not a very accurate one.

Q. All right. Could you do a rough one?

A. I would hesitate to do so.

Q. Could you do one using figure DDX a rough estimate using figure DDX 58?

A. I think it would take a considerable amount of time, and it's not something that's normally done by hand. It's usually done with computer software.

Q. In your opinion, would the -- should the area under the curve, under each curve of figure one [119] add up to 100 percent of molar -- of total mass?

A. I believe I answered that before when I said that if 100 percent of the mass was considered in the construction of the figure, it should have been 100 percent.

Q. Is 100 percent of the mass considered in figure one?

A. There's no indication of 100 percent.

Q. You don't know?

A. No.

Q. Nothing in the patent tells you whether it is or not?

A. I'm not exactly sure what you're getting at here, but the -- what the question actually is, but if I understand it correctly, I don't recall that there is.

Q. Assuming that all the mass was considered under the curves in figure one, should that add up to 100 percent?

A. If the curve was constructed correctly and all the data is available, it should be very close. Within the error that's inherent in any process.

Q. Is your answer the same for figure two?

A. Well, figure two does not plot the mass.

[120]

Q. Should the area under the curve figure two add up to approximately 100 percent molar fraction?

A. It should add up to approximately that. You have to appreciate that these are not particularly rigorously-generated curves in my opinion.

Q. You mean figure one and figure two?

A. They were generated to a certain tolerance, which I was not -- I'm not aware of what the tolerance is. I mean...

Q. I was asking you earlier about the percent difference between your opinion of the peak and the stated average molecular weight in figure one. And I have a more regular calculator for you. Could you please calculate for me the difference between your measurement as stated in your opinion in paragraph 62 for the 7.7 kilodalton curve?

A. Okay. So I'll point out that the molecular weight in the legend to the curve says 7.7. And

molecular weight that is stated as being measured is 6.8. So one way of doing it is to take 7.7, subtract 6.8, which is the difference between the two. And as a percentage being a portion of the whole, divide by 7.7, that equals 11.7 percent.

Q. And is another way of doing that to divide [121] that difference by 6.8?

A. Well, I don't think that adequately reflects the -- the error in the weight that was expressed in the legend.

Q. Would that also be a measurement of the differential between where you measured the peak and the statement in the legend?

MS. HOLLAND: Objection to form.

A. Repeat, please.

Q. (By Mr. Aannestad) Would that also be a measurement of the differential between where you measured the peak on that curve and the statement in the legend?

A. The difference between the two is a measure of the differential. If you asked me to compute the percentage error, it has to be based upon the expressed number, not based upon the experimentally-or manually-derived number.

Q. What is the error in your calculation for the twelve kilodalton curve?

A. I'll do it the same way, except it's not --there we go. 8.3 percent.

Q. What is the error for the twelve kilodalton curve based on your marking today on DDX 58?

[122]

A. 16.7 percent.

Q. Is that an acceptable margin of error to you?

A. The target margin of error was not mentioned, but I believe that in my opinion to a person skilled in the art for this purpose, that's close enough.

Q. In your opinion, that's close enough for a person of skill in the art to assume the meaning peak molecular weight for the purposes of the patent disclosure?

A. My opinion is as stated in the -- in the declaration. A person of skill in the art would have understood that the peak positions on the curves were within a margin of error with the corresponding identified average molecular weights.

(Court reporter interruption.)

A. Corresponding identified average molecular weights.

Q. (By Mr. Aannestad) Standing alone, if you were only relying on figure one, would that still be your opinion that a person of skill in the art would assume that average molecular weight means peak molecular weight?

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Q. You would be willing to assume that?

MS. HOLLAND: Objection to form.

A. I believe I just said that.

Q. (By Mr. Aannestad) Looking at your first sentence of paragraph 63, can you please read that sentence for the record?

A. "A person of skill in the art, knowing that there are other average molecular weights that are used to describe polymers, could also have considered the possibility that the term 'average molecular weight' refers to the number average molecular weight Mn or weight average molecular weight Mw."

Q. By "could," do you mean would?

A. No, I mean "could."

Q. So you don't -- in your opinion, a person of skill in the art would not necessarily have considered the other types of ave -- or the -- I'm sorry, would not necessarily have considered average molecular weight or number?

A. Not necessarily.

Q. Please read the next sentence.

A. "However, a person of skill in the art would have understood that, on a molecular weight distribution curve, Mn typically is smaller than Mp."

[125]

Q. How much smaller?

A. Impossible to say.

Q. Well, what's typical?

A. Typical is that it often happens that way.

Q. So it's impossible for you to say how much smaller Mn typically is than Mp?

A. It depends on each specific instance.

Q. Can they be the same?

A. They can be.

Q. Do you know if they're the same in the case of figure one?

A. No, I do not.

Q. They could be the same?

A. Since it's possible for them to be the same, they could be the same.

Q. Please read the next sentence.

A. "Therefore, if the 'average molecular weights' referred to in Figure 1 were Mn, the person of skill would have expected the peak on the curve to have a higher value than 7.7 ... not a lower value."

Q. What do you mean when you say "higher"? How much higher?

A. I do not make a judgment as to how much.

Q. Could be slightly higher?

[126]

A. It could be.

Q. Could be not higher at all?

A. It could be.

Q. Did you try to calculate this?

A. I said before that I think that to do it appropriately you need the original chromatogram, which I do not have.

Q. Did you think about trying to calculate it?

A. I did think about it.

Q. Why didn't you do that?

A. Because I didn't think it would be very accurate. I did a few back-of-the-envelope type things, but I don't think it's an accurate way to do it.

Q. Do you recall what your conclusions were from your back-of-the-envelope calculations?

A. No, I do not.

Q. Do you recall whether they supported your opinion?

A. I believe that they did.

Q. But you don't know?

A. I don't have them in front of me and it was done sometime ago.

Q. So is it your opinion that because the [127] number average molecular weight would have reflected error in the opinion -- or in the figure, a person of ordinary skill in the art would not have relied on the figure to conclude that average molecular weight means number average?

MS. HOLLAND: Objection to form.

A. I've already stated that my opinion is --is that the average molecular weights given in the legend do not refer to number average molecular weight.

Q. (By Mr. Aannestad) Why is that?

A. Well, because again, in the declaration it's expressly stated that in the prosecution average molecular weight refers to peak molecular weight. And as I said before, there's no indication that a number average or a weight average molecular

weight was calculated based upon what is present in the patents.

Q. Focusing on paragraph 63, can you explain to me why you believe a person with skill in the art would not have understood the average molecular weight to refer to number average?

A. Would not have understood?

Q. Correct.

A. Or would have understood that the number - [128] the the average molecular weight does not refer to number average molecular weight?

Q. Correct.

A. Because there's no indication to suggest that it does.

Q. Is there any indication to suggest that it's peak average?

A. Yes, because peaks are presented.

Q. Is your opinion based on the fact that there would be a greater difference between the stated average molecular weight in the legend and where you believe number average might be?

A. These are generalities. I have no way to come up with a quantity for you.

Q. In paragraph 64 where you say the weight average molecular weight would be significantly larger than the average molecular weights, what did you mean by "significantly larger"?

A. I meant it would be larger, and I made the conclusion that it would be significant.

Q. What was that based on?

A. Based upon what I know about the relation between -- the general relation between number average, peak average, and weight average molecular [129] weight.

Q. Do you have any way to quantify that?

A. If I had the original chromatogram I could calculate it.

Q. You don't have that, do you?

A. No, I do not.

Q. You didn't ask for that, did you?

A. No, I did not.

Q. Did the lawyers ask you to not calculate mole weight average molecular weight?

MS. HOLLAND: This is -- this is a communication from counsel. I guess if we didn't ask him then there wasn't a communication, so he can answer the question. If we didn't -- can I -- let me read that again.

There's an agreement about communications from counsel, but I believe since this was not a communication that he can answer the question.

MR. AANNESTAD: Okay.

A. The lawyers did not ask me to not calculate the molecular weight.

(Court reporter interruption.)

A. The molecular weight. I'm sorry.

Q. (By Mr. Aannestad) Please read the

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A. I don't understand your question.

MS. HOLLAND: I don't I think it's I think the question is ambiguous because it -- what's said in paragraph 64 is not inconsistent with what's in the -

Q. (By Mr. Aannestad) Well, the '847 patent may not literally have the --

MS. HOLLAND: I think that's

Q. (By Mr. Aannestad) -- quotation average molecular weight, correct? But that phrase in your opinion means -- or the -- the phrase "copolymer-1 having a molecular weight" means average molecular weight, doesn't it?

A. No. I say that copolymer-1 molecular weight means average molecular weight in my declaration.

Q. Uh-huh.

A. And that's what I mean.

Q. Okay. And there is a claim in the '847 patent that has that phrase copolymer-1 having a molecular weight, correct?

A. That's correct.

Q. And that means average molecular weight, doesn't it?

[135]

A. My declaration says what it says, and I do not believe that the '847 patent contains the term "average molecular weight."

Q. But it does contain a term that means average molecular weight, doesn't it?

A. According to my declaration, copolymer-1 having molecular weight means copolymer-1 having an average molecular weight.

Q. So the answer is yes?

A. No, the answer is not yes because average molecular weight does not appear in the '847 patent.

Q. But does a term that means average molecular weight appear in the '847 patent?

A. According to the declaration, it can be construed to be that way.

Q. Does that change your opinion at all?

A. No, it does not.

Q. In your opinion, would a person of skill in the art reviewing the prosecution history of the '847 patent understand that that patent relates to average molecular weights?

A. Within the context of everything that we've said today, I believe that it would. But again, I have not read the '847 patent in some time.

[136]

Q. Is it your understanding that the specification of the '847 patent is any different than the specification of the '808 patent?

A. I believe I said in the declaration that the specifications in all the patents-in-suit were essentially the same.

Q. And looking at pages three and four of Exhibit DDX 59, do you have any basis to believe that that is not an accurate representation of the claims of the '847 patent?

A. The -- what is stated here?

Q. Correct.

A. Without comparing it directly to what is in the '847 patent, I have no reason to believe that it is or it isn't.

MS. HOLLAND: I'm sorry to interrupt, Anders, but I think the confusion is that I don't know that when you handed this to Dr. Grant he -- he understood where it was coming from and that it was attached to a declaration submitted, so --

MR. AANNESTAD: Okay.

MS. HOLLAND: -- that might be the confusion.

Q. (By Mr. Aannestad) Exhibit 4 is -- well,

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average molecular weight, correct?

MS. HOLLAND: I think it's been asked and answered. You can answer again.

A. Well, I will answer again that I believe paragraph 51 55, if I can find it, states that, "A person of skill in the art would have understood that

'copolymer-1 having a molecular weight' means copolymer-1 having an average molecular weight."

Q. (By Mr. Aannestad) Did you have that in mind when you wrote paragraph 64?

A. Yeah, I believe I did.

MS. HOLLAND: When you get to a convenient breaking point, we can take lunch.

Q. (By Mr. Aannestad) Specifically, did you have that in mind when you rendered your opinion in the parenthetical in paragraph 64?

A. In the parenthetical which is?

Q. "Which does not include any claim that recites 'average molecular weight'"?

A. Again, I have to state that I do not believe that the word "average molecular weight" appears in that patent.

Q. But you didn't point out to the Court that that patent includes claims with a term that means [139] average molecular weight, did you?

A. I did in my declaration.

Q. Did you do that in paragraph 64?

A. I didn't believe it was necessary since it's in my declaration.

Q. It was -- it should have been obvious to somebody?

A. It's in the declaration.

MS. HOLLAND: Object to form, argumentative.

MR. AANNESTAD: Okay. Okay. Why don't we take lunch.

MS. HOLLAND: Okay.

VIDEOGRAPHER: We're going off the record at 12:34 p.m.

(WHEREIN, a lunch recess was taken from 12:34 p.m. to 1:24 p.m.)

VIDEOGRAPHER: We're back on the record at 1:24 p.m.

Q. (By Mr. Aannestad) Good afternoon, Dr. Grant.

A. Good afternoon.

Q. Returning to your declaration, paragraph 64. Is it possible that the weight average [140] molecular weight could be the same as the peak molecular weight?

A. That's a little bit more of an intricate question to answer. I don't think that it is, but I don't want to go on record as saying absolutely it's not.

Q. Before lunch we were talking about the statement during prosecution in the '847 patent about average molecular weight meaning weight average molecular weight, correct? Do you recall that discussion?

A. No, we did not, in my recollection.

Q. Okay. Well, we were leading up to that with the '847 patent, I guess. So I'll -- I'll just withdraw that.

Could you please read the sentence that starts, "Although, during the prosecution"?

MS. HOLLAND: I think that's been read into the record already. But go ahead.

A. Okay. "Although, during the prosecution of the '847 patent (which does not include any claim that recites 'average molecular weight'), the applicants stated that 'kilodalton units implies a weight average molecular weight,' (see the '847 patent prosecution

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course, depends to a certain extent on the shape of the peak, the curve, and it's difficult to generalize for all curves. But for curves that are in the patent that we're dealing with, I think that it's a reasonable statement to make.

Q. And what is that based on?

A. It's based on my -- my knowledge, my experience, my reading.

Q. Did you do any calculations?

A. Of what?

Q. Of where weight average would be on the data set represented by figure one?

A. I believe I stated earlier that I did some preliminary I think I called them back-of-the-envelope calculations. They were not detailed calculations.

Q. Why didn't you include those calculations in your declaration?

A. Didn't feel that it was necessary to state my opinion.

Q. Would it have been possible to do a more detailed calculation?

A. Again, as I stated before, I think that the correct way to do the calculation is with the original [143] primary data and not with the information in figures one and two. But it would be possible to do a calculation on the figure, but I don't know how accurate it would be.

Q. And because weight average molecular weight in your opinion would be different than the average molecular weight stated in the legend, you conclude that those do not refer to weight average molecular weight?

A. I -- I believe that it is very likely that that is the case, and that's the reason that I do not think the legend refers to weight average molecular weight.

Q. Because they're different?

A. Because they are -- yes, because they are different.

Q. The same with number average molecular weight, because that's different you do not conclude that the average molecular weight refers to number average?

A. Well, I do not rely on that alone. As I stated before, I rely on all of the information that was presented to me to form my opinion, and that's only part of it.

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Q. The other part is the prosecution history?

A. No. The other part is the fact that there is no information regarding any attempt was made to compute number average or weight average.

Q. And there's also no information regarding an express statement of peak molecular weight being the average molecular weight, correct?

A. There is in the prosecution.

Q. But nowhere in the patents?

A. To my recollection, no.

Q. Let's talk about the prosecution. In paragraph 64 you discuss the statement to the PTO that average molecular weight means weight average molecular weight, correct?

A. No. It states that kilodalton units imply weight average molecular weight.

Q. Okay. And then paragraph 65 discusses the instance in the '539 prosecution where Teva told the patent examiner that average molecular weight means peak molecular weight, correct?

A. I believe that's what it says, yes.

Q. Okay. Are you aware of a third instance where Teva told the PTO that average molecular weight had a third meaning?

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Q. So 1.6 would be rounded to two?

A. In general, yes.

Q. 2.4 would be rounded to two?

A. In general, yes.

Q. But 2.6 would be rounded to three?

A. Yes.

Q. What do you mean by the word "complex" in "a complex mixture of polypeptides"?

A. I mean that is not simple, it is not easy to discern or understand, and is composed of a relatively large number of different components.

Q. Anything else?

A. I mean, I believe that that's sufficient. I might think of something later, but that's -- that's what I want to say.

MR. AANNESTAD: Okay. I think we need to change the tape.

VIDEOGRAPHER: We're going off the record at 2:10 p.m.

(WHEREIN, a recess was taken.)

VIDEOGRAPHER: We're back on the record on tape four at 2:27 p.m.

Q. (By Mr. Aannestad) Returning back to your declaration, please turn to paragraph 51. Could you

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my declaration is what I have discussed.

Q. Turning to paragraph 53. Do you see the statement there, "For essentially the same reasons stated in paragraph 52"?

A. Yes, I do.

Q. Are there any additional reasons in paragraph 53 that are not discussed in 52?

A. I believe that that statement implies that what is in 52 is in 53.

Q. Please turn to paragraph 60. Do you see your reference to Flory there?

A. I do.

Q. Who is Flory?

A. I do not know him personally. He is a person that wrote a book on polymer chemistry.

Q. Is he well-known in polymer chemistry?

A. I don't know if he is or not.

Q. Did you find this reference to Flory or was that provided by Teva's lawyers?

A. The reference was provided by -- I -- I did not provide this reference myself.

Q. Was it provided by the lawyers?

A. It was provided by -- actually, I don't know who it was provided by. It was provided by the [176] group that I was in discussion with.

Q. Who was the group?

A. You want names? Is that what you want? I mean --

Q. Yes.

A. -- am I allowed to divulge communication?

MS. HOLLAND: I -- I think that I'm not sure that you're not talking past each other. I believe he means the group of lawyers he was working with.

THE WITNESS: Yeah.

Q. (By Mr. Aannestad) Right, yeah. But the names is fine.

MS. HOLLAND: Yeah, the names of the lawyers is okay, but the -- the actual substance of the communication.

A. Okay. The best of my recollection there were William James, Michelle Shen, and at times Patrice Jean.

Q. (By Mr. Aannestad) You cite page 317 of Flory, correct?

A. That's what it says, yes.

(WHEREIN, Exhibit DDX 61 was marked for identification by the Court Reporter.)

[177]

Q. (By Mr. Aannestad) You've been handed DDX 61, which is a copy of some pages from the text of Flory. And you'll do you see page 317 there?

A. I do.

Q. Is that the page that you cite?

A. I believe that it is. Since I don't have the appendices, I do not have it to compare directly.

Q. Please turn to the next page, page 318. Did you review page 318 previously?

A. No, I did not.

Q. Did you review page 317?

A. Yes, I did.

Q. But you didn't continue reading on to page 318?

A. No. Page 317 met my purposes.

Q. Okay. Would you please read the first sentence of the first paragraph on 318 that starts "The experimental approach" for the record?

A. "The experimental approach to the problem of molecular weight distribution, involving separation of the polymer by fractional precipitation into fractions covering comparatively narrow molecular weight ranges followed by reconstruction of the distribution curve from the amount and average [178] molecular weight of each fraction, is laborious to say the least, and the results which have been obtained in this manner are only semiquantitative."

Q. Referring to the portion of that statement that describes the reconstruction of the distribution curve from the amount and average molecular weight of each fraction, would you agree with that description of the experimental approach to molecular weight distribution?

MS. HOLLAND: Do you have a time frame on that?

Q. (By Mr. Aannestad) Well, do you agree today? Do you agree that that's an accurate statement?

A. Well, I -- I find things in that statement that I do not believe relate directly to the patents-in-suit.

But I will concur that to do what he is describing is a laborious task.

Q. And that involves determining the average molecular weight of each fraction; is that correct?

MS. HOLLAND: Objection to form.

A. Well, he talks about fractions covering comparatively narrow molecular weight ranges. So it becomes more or less laborious depending upon how many [179] different fractions and how large the range is, and he doesn't specify.

Q. (By Mr. Aannestad) But if you have a range, then what you're measuring is the average molecular weight in that range, correct?

A. If it is a mixture and depending upon the method you use to measure it, that could be correct.

Q. Have you ever reviewed the declaration of Dr. Svec on claim construction?

A. If you mean by review have I read it?

Q. Yeah.

A. Yes, I have.

Q. Do you disagree with any portions of it?

A. I do.

Q. What are your disagreements with it?

A. I would like to have it to look at and point them out.

(WHEREIN, Exhibit DDX 62 was marked for identification by the Court Reporter.)

Q. (By Mr. Aannestad) You've been handed Exhibit DDX 62, a copy of the declaration of Dr. Svec on claim construction without exhibits.

A. Okay. First of all, paragraphs one to thirteen describe his qualifications and his --

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[191]

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A. Well, paragraph 27 actually doesn't really stand on its own. I mean, because it involves information from other paragraphs. But he says because the "molecular weights of copolymers vary depending upon the measurement technique."

Actually, what varies is the number that results from the analysis of the copolymers depending upon the measurement technique. And he claims that that makes them further ambiguous. But I'm not sure that I know what he means by "further ambiguous."

If it's a legal term, I'm not capable of rendering an opinion. But he says earlier that it's a -- a complicated question for such mixtures. I agree that it is a complicated question for mixtures, and if that's what makes it ambiguous, then I guess that's what he's trying to say. But I just have trouble understanding what he means by that paragraph.

Q. Well, given the -- given a clarification that the molecular weights of copolymers means the --the numbers -- as you state, the numbers of the molecular weights vary?

A. Uh-huh.

Q. Do you disagree with that?

MS. HOLLAND: I I'm going to object. I

[193]

it, in paragraph 38 of my declaration, "For example, when a sample of a polymer is measured by osmometry, the molecular weight obtained is a number average molecular weight (commonly referred to as 'Mn'), which represents the total weight of the sample divided by the total number of moles of molecules which it contains. On the other hand, when a sample of polymer is measured by MALLS," M-A-L-L-S, "the larger molecules will make a greater contribution to light scattering than an equal amount of smaller ones, and the molecular weight obtained is a weight average molecular weight."

So going back to his statement that because molecule weights of copolymers vary depending upon the measurement technique, which is what I said in my declaration, a condition used, the claims are ambiguous. I don't see how it follows from that that the claims are ambiguous because that is inherent in the techniques.

Q. Because depending on the technique used you might know which average molecular weight is being determined?

A. Certain -- certain techniques because of what is measured, the way they're performed, the [194] physical characteristics of the methodology are known to produce specific types of average molecular weights. Other techniques can produce one or more.

Q. Such as size exclusion chromatography?

A. Such as size exclusion, yes.

Q. And what about the conditions, would that also vary the numbers of the molecular weights?

MS. HOLLAND: Objection to form.

A. I'm not sure that conditions is the word you want to use. I mean, what I would say is that the composition of the polymers will cause the numbers to vary.

I suppose that it is possible that if you change the condition such as the temperature, the pressure, and things like that, you may well come up with a different number. It is usually common practice that the conditions are stated and it is understood that those conditions must be met for reproducibility.

Q. (By Mr. Aannestad) Is flow rate one of those conditions?

A. It can be.

Q. What about the elution buffer?

A. The elution buffer may have an effect.

[195]

Q. What about the pH?

A. The pH may have an effect.

Q. How about the salt?

A. The salt may have an effect.

Q. The choice of column?

A. The choice of column may have an effect.

Q. What about the packing density?

A. Insofar as the packing density will influence the resolution, it may have an effect.

Q. And the particular standards used would have an effect as well, correct?

(Court reporter interruption.)

Q. (By Mr. Aannestad) And the particular standards would have an effect as well?

MS. HOLLAND: Objection to form.

A. If the column were calibrated correctly, it should produce a reasonable molecular weight.

(Court reporter interruption.)

A. Molecular weight. I'm sorry.

Q. (By Mr. Aannestad) Anything --

A. Let me continue here.

Q. Anything else about paragraph I guess 27?

A. No.

Q. Okay.

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[203]

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Q. (By Mr. Aannestad) The peaks in figure two are not at the same points on the X axis as in figure one, correct?

A. That is correct.

Q. Should they be?

A. I don't believe so.

Q. Why not?

A. Because each figure is depicting a different parameter or characteristic of the mixture. And those parameters are not equal to each other.

Q. Could you determine the peak molecular weight from figure two?

A. Yes.

Q. What is the peak molecular weight of the curves in figure two?

A. You want me to do it just by what we colloquially refer to as by eyeballing

Q. Yes.

A. -- just by looking at it? The two designated 7.7 appear to be close to what represents the 5,000 tick, and the one designated 12.0 appears to be a little bit lower than that. Is that sufficient?

Q. Yes. Yes. Why is the peak molecular weight of the 12,000 curve lower than the peak [204] molecular weight of the 7.7 curves?

A. Because the molar fraction distribution differs between the two.

Q. Is the peak molecular weight you're reading from figure two the same peak molecular weight as you read from figure one?

A. No, it is not.

Q. How is it different?

A. Well, it's different because what you read is different.

Q. Does it provide different information?

A. It does provide different information because the Y axis are different.

Q. How many different peak molecular weights are there?

MS. HOLLAND: Objection to form, ambiguous.

A. Each peak has a peak molecular weight.

Q. (By Mr. Aannestad) So in figure two, the peak molecular weight of the twelve kilodalton curve is actually lower than 5,000 daltons, correct?

A. Yes.

Q. And in fact, it's lower than the peak molecular weight of the 7.7 kilodalton curve?

A. It appears that it is slightly.

* * *

[210]

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MR. AANNESTAD: Well, this is part of the portions that are cited by Teva and Dr. Grant in the claim construction filings. Column two, 29 through 40 are cited. So I directed him to the line 29 for context. I want to know what is meant by what that particular sentence refers to.

A. Can you point out to me where that citation is?

Q. (By Mr. Aannestad) Paragraph 35 of your declaration. Citation there in parentheses, "e.g., the '808 patent, col. 2, lines 29-40."

MS. HOLLAND: Again, this is in the context of the background section, so I hope you're -- I mean, he

can answer this question. But I don't know where you're going with this, so we'll have to see.

A. I believe that this simply points this out as an example of producing copolymer-1 of molecular -- a lower molecular weight by removing undesired higher molecular weight species, which is what is stated in the patent.

Q. (By Mr. Aannestad) Does that sentence make any statement about directly making low molecular weight copolymer-1 versus first making larger molecular weight and then reducing the size?

[211]

A. It says, "The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration."

(Court reporter interruption.)

A. Dialysis or ultrafiltration. And that is what is referred to in paragraph 35 as a way of making it by removing undesired high molecular weight species.

Q. (By Mr. Aannestad) What is partial acid or enzymatic hydrolysis?

A. In the context of polypeptides, hydrolysis refers to breaking the polypeptide bond, and if you do not break every polypeptide bond in the polypeptide, it is partial. And two ways that can be used to break

polypeptide bonds is by using a specific enzyme or by using acid.

MR. AANNESTAD: I think we need to change tape.

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VIDEOGRAPHER: We're going off the record at 4:11 p.m.

(WHEREIN, a recess was taken.)

VIDEOGRAPHER: We're back on the record on tape five at 4:13 p.m.

Q. (By Mr. Aannestad) Does the sentence in column two from lines 3 6 through 4 0 make any additional statement regarding producing low molecular weight copolymer-1, other than starting with a higher and reducing it?

A. Well, it says the "further method."

Q. Is that method described?

A. It's not described in great detail, but the underlying idea is presented.

Q. Are there any details of exactly how to do that provided?

MS. HOLLAND: In that paragraph you mean?

Q. (By Mr. Aannestad) In that -- we can start within that paragraph.

A. No, I believe it's just a general statement.

Q. Are you relying on that sentence in any way for an opinion that copolymer-1 should not be construed to include synthesized by chemically

[Exhibit 1 to the Declaration of Carolyn A. Blessing]

UNITED STATES
DISTRICT COURT
SOUTHERN
DISTRICT OF
NEW YORK

TEVA
PHARMACEUTICALS
USA, INC.,
TEVA
PHARMACEUTICAL
INDUSTRIES
LTD., TEVA
NEUROSCIENCE,
INC.,

and

YEDA RESEARCH
AND DEVELOPMENT
CO., LTD.,

Plaintiffs,

vs.

SANDOZ, INC.,
SANDOZ
INTERNATIONAL
GMBH, NOVARTIS
AG,

Defendants.

NO. 08 CV 7611 (BSJ)

_____/

VIDEOTAPED DEPOSITION
OF FRANTISEK SVEC, Ph.D.
SAN FRANCISCO, CALIFORNIA
WEDNESDAY, OCTOBER 28, 2009

[245]

Q. right?

A. Yes, that's what --

Q. Now, the peak molecular weight comes right off the chromatogram; correct?

A. Not -- not really, because out of the chromatogram comes the elution time, you know, so you cannot say immediately that this is the peak molecular weight -- the peak of curve that goes out of the system.

Q. Right.

If you have a calibrated column, you can read the molecular weight off of the chromatogram; correct?

A. If you have a calibrated column with the elution volumes trans- -- transferred to -- to molecular weights, then you can do what we did here with the Figure 1 and Figure 2, and see what the the peak molecular weight could be.

Q. Okay. So in that sense, this size exclusion chromatography technique will give you the peak molecular weight?

A. It will give you peak molecular weight, weight average molecular weight, and number average molecular weight, if done properly.

Q. Okay. Now, how does the size exclusion [246] chromatography technique give you a number average and a weight average molecular weight?

A. Well, this does not give you these values directly. You have to calculate them from -- from the -- from the curve.

Q. Right.

It doesn't -- the size exclusion chromatography technique doesn't give you those average molecular weights. You calculate them using the data that's generated from the chromatogram; correct?

A. Well, it's -- it's a little bit playing with words, of course, because, essentially, you are getting the data from results you are obtaining from the size exclusion chromatography, you know, so --

Q. Assume you didn't have a computer in 1994. Would you say that size exclusion chromatography would give you a number average molecular weight?

A. Yes, you can always --

Q. You can calculate it?

A. -- calculate it.

Q. But does it give it to you?

A. Well, it depends how we -- what we -- what we call "give" and "calculate," you know, so at the end [247] of the -- the measurement and perhaps the calculation, you are getting these three different values.

Q. You can calculate the number average and weight average

A. Yes.

Q. -- and you have the peak molecular weight; correct?

A. That's right.

Q. In paragraph 38, you say, "There is nothing in the specifications of the patents-in-suit that would require one of ordinary skill in the art to understand that peak average is used." Do you see that?

A. Yes, I do.

Q. Now, is it your understanding that the legal requirement for indefiniteness is that the patent requires a certain meaning of a -- of a claim term?

MR. KRAMER: Objection.

THE WITNESS: Please, correct me if I do not repeat your question correctly.

You're saying that the indefiniteness or -- or definiteness of the patent requires to have a certain amount of information there.

MR. JAMES: I'm sorry. I did ask you a

[Exhibit F to the Declaration of Anders T. Aannestad]

UNITED STATES
DISTRICT COURT
SOUTHERN DISTRICT OF

NEW YORK

TEVA
PHARMACEUTICALS USA,
INC.,
TEVA PHARMACEUTICAL
INDUSTRIES
LTD., TEVA NO. 08 CV 7611 (BSJ)
NEUROSCIENCE, INC.,

and

YEDA RESEARCH AND
DEVELOPMENT
CO., LTD.,

Plaintiffs,

vs.

SANDOZ, INC., SANDOZ
INTERNATIONAL GMBH,
NOVARTIS
AG,

Defendants.

_____/

[183]

Q Did you attempt to calculate the weight average molecular weight

A From this?

Q -- of those curves?

A No, I did not, because--

Q Did not?

A -- it's impossible.

Q So before you--why is it impossible?

A How do you -- I -- I really don't have any significant -- any individual points, so it -- this curve doesn't allow me to -- to calculate the average -- the weight average or number average.

Q Before you rendered your opinion saying that the claim terms were indefinite, you didn't attempt to calculate a weight average molecular weight or number average molecular weight from Figure 1; did you?

A I didn't attempt doing this because this -- this would be -- this -- this -- this is not possible to do that. That's how -- there was no reason why I should attempt this simply because this is -- this is impossible to do.

Q Why is it impossible?

A Because you don't have data. You know, this is -- this is just a curve, you know, and how can I [184] get any good data to do the calculations, you know. The curve doesn't look like being really drawn

in a way that would allow anything like that, you know. You need to have hard data.

Q What kind of hard data?

A I mean, for this, you need to have -- for example, if this would be done by a computer, then you would have to use the computerized system, the computer system to use all the -- the programs it has built in to do the calculations, you know. By definition, the molecular weights are essentially sums of numbers or weights of the individual components there, divided by the overall number or weight of -¬of the polymer. We don't have this data here.

Q Well, you have the -- the percentage of the total mass at the molecular weights that are shown on the X axis; correct?

A Well, I -- yes, said -- this is what it says, but my impression is that these numbers are wrong.

Q What's your impression based on?

A It's based on the simple fact that we discussed earlier today that the area beneath this curve should be 100 percent. Cannot be any more, right. So if we try to calculate what the area is, [185] and I tried, then it comes about ten times off. You get about 1,000 percent, you know. So obviously these numbers are wrong.

Q If the data in Figure 1 were produced with a -- well, let me strike that.

If you were to use the shape of the curve and the relative heights at -- at the -- at data points over the

-- over this curve, could you calculate the number average and weight average molecular weight?

A Not from this curve.

Q Impossible?

A Impossible.

Q Now, earlier we looked at a reference that you had drafted, or that you had published, where the number average molecular weight was to the left of the peak of the polymer distribution curve; correct?

A Yes.

Q And if -- if you were to assume for a moment that the number, for example, in the 7.7 -- for 7.7 -- let me strike that.

If you were to assume for a moment that the 7.7 number in the legend is the number average molecular weight, okay --

A Okay.

* * *

[Exhibit 3 to the Declaration of David C. Doyle]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC.,	)	
and	)	
YEDA RESEARCH AND DEVELOPMENT CO., LTD.,	)	
Plaintiffs,	)	
vs.	)	Civil Action No. 08 CV 7611 (BSJ)(AJP) ECF Case
SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG,	)	
and	)	
MOMENTA PHARMACEUTICALS, INC.,	)	
Defendants.	)	

VIDEOTAPED DEPOSITION OF
GREGORY A. GRANT, PH.D.
TAKEN ON BEHALF OF THE DEFENDANTS
SANDOZ, INC. and MOMENTA
PHARMACEUTICALS, INC.

OCTOBER 28, 2009

[9]
Q. And your counsel may object to some of my questions today, but do you understand that unless she instructs you not to answer, you still need to answer that to the best of your ability?

THE WITNESS: Is that correct?

MS. HOLLAND: Yeah. Of course, if there's a matter of privilege or a matter that is not discoverable, you would exclude that from your question?

MR. AANNESTAD: Well, if -- right. Well, I mean, if you instruct him not to answer, then he won't answer.

Q. (By Mr. Aannestad) But otherwise -- my point is that doesn't mean you don't answer the question if there's an objection that may be for the record.

A. If that's agreeable with my attorney, yes, I understand.

Q. Is there any reason why you cannot give your full, complete, and truthful testimony today?

A. I do not believe so.

Q. What did you do to prepare for your testimony today?

A. Could you be a little bit clearer about

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[15]

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A. It means an average molecular weight of a mixture.

Q. What is an average molecular weight?

A. It's a molecular weight that is arrived at by considering the properties of the components.

Q. Of a mixture?

A. It can be a mixture, or most often a mixture, yes.

Q. For polymers are there more than one type of average molecular weight?

A. Yes, there are.

Q. What different types are there?

A. To the best of my knowledge, there are peak average molecular weight, number average molecular weight, weight average molecular weight, Z average molecular weight, and viscosity average molecular weight.

Q. Is peak molecular weight actually an average?

A. It's often termed an average, but in practice it really is simply the molecular weight at the peak.

Q. So it's not actually an average, is it?

MS. HOLLAND: Objection to form, asked and [16] answered.

A. I wouldn't say that it -- it's not actually an average because it depends upon how the viewer is considering it.

Q. (By Mr. Aannestad) What way does it depend on how the viewer is considering it?

A. Whether or not the viewer is considering only the single point at the apex of the curve, or whether the viewer is also considering points on either side of that apex.

Q. How does considering points on either side of the apex make that an average?

A. Because once you consider more than one point and you come up with a single number, you are in effect averaging.

Q. Okay. But if you are looking at peak molecular weight only ¬

A. Uh-huh.

Q. -- is that an average?

A. I would say that in the truest form it probably is not.

Q. So in truth, peak molecular weight is not an average molecular weight?

MS. HOLLAND: Objection to form, [17] mischaracterizes the testimony.

A. It is often referred to as an average molecular weight in the literature.

Q. (By Mr. Aannestad) But in truth, it is not, is it?

MS. HOLLAND: Objection to form.

A. If one is using the apex of the curve to express the peak average molecular weight, in truth it is not a real average.

Q. (By Mr. Aannestad) Do you refer to peak molecular weight as an average in your literature?

A. I do not recall whether I've done so.

Q. Do you ever recall having done that?

A. I do not recall. I have a great deal of literature going over many years.

Q. About how many papers have you published?

A. Over a hundred. Again, I don't recall the exact number, but it's -- if you consider invited articles, it's in the vicinity of 120.

Q. How about book chapters?

A. I've edited two books and I have written chapters in each of them.

Q. And lectures, do you give lectures?

A. I have given lectures in the past. I do

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[24]

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Q. Do you do calculations in your work at PNACL of percent mass of the polymer mixture?

A. I may have in the past. Again, I -- I don't do this routinely unless I'm asked to do it.

Q. So that's not work that routinely comes up in your role directing the PNACL?

A. That is correct.

Q. Paragraph four where you say, "I have used this technique" referring to SEC, "to measure the

molecular weights of proteins." What do you mean by you have used the technique? How many times?

A. I've used it a large number of times and I cannot tell you an exact number.

Q. In your analytical work at the PNACL, do you ever do calculations of area under the curve?

A. We have software that is capable of doing that.

Q. Are you capable of doing that yourself by hand?

A. I think that I am, but I do not remember the last time that I did it.

Q. You're familiar with that type of calculation, though?

A. Yes.

* * *

[54]

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MS. HOLLAND: Objection to form. Is that a question?

Q. (By Mr. Aannestad) Describe what you mean.

A. My ordinary use of the term "relative" means when one thing is compared to another.

Q. Are average molecular weights of polymers like copolymer-1 compared to a standard?

A. That's not what this footnote refers to.

Q. But is that true?

A. Could you repeat the question?

Q. Are the average molecular weights of polymers like copolymer-1 generated by comparison to a standard?

A. I believe that the numbers are derived by comparison to standards.

Q. Are they also dimensionless quantities?

A. Molecular weights technically are dimensionless quantities.

Q. Why is that?

A. Because that's the science.

Q. What do you mean "that's the science"?

A. I mean, that's -- that's what I have been taught and that is what is in the literature. And that is what other scientists who have gone before me [55] have determined.

Q. Is it because they're relative it doesn't really matter what the dimension is; it's a relative number?

A. It's because you're talking about a number and not about a mass.

Q. What's the second part of that statement?

MS. HOLLAND: Objection to form.

A. Well, the second -- what I was referring to after "relative" was the statement of dimensionless.

Q. (By Mr. Aannestad) Okay. Please discuss -- describe that for me.

A. I believe we've already discussed that.

Q. Please turn to paragraph 26 of your declaration. Do you see the first sentence there referring to molar fraction?

A. Yes, I do.

Q. What are the units of a molar fraction?

A. Molar fraction does not have a unit because it is a relative quantity.

Q. Please turn a number of pages to paragraph 34. It's on page fourteen. What do you mean by the phrase "a specific kind of polymer [sic]" in the first sentence of paragraph 34?

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[63]

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weight?

A. If each fraction contains more than one species.

Q. And a fraction of copolymer-1 would contain more than one species, correct?

A. It could.

Q. Do you have any basis to believe that it would not?

A. It depends to how highly resolved the fractions are.

Q. In your opinion, is it possible to resolve a fraction of copolymer-1 that contains only one species?

A. It may be, but I wouldn't know unless I actually tried to do it.

Q. But if there's more than one species in that fraction, then that is a measurement of an average, correct?

A. If there is more than one species in the fraction and you come up with a single number to describe it, it is an average.

Q. Is it possible there would be species in that fraction that are -- I'll ask that later.

Looking at paragraph 39, do you see the [64] statement that "The values for Mn and Mw can be further calculated using the size exclusion chromatography

data"?

A. I do.

Q. How is that done?

A. Which one?

Q. Let's start with Mn.

A. The size exclusion chromatography data relates the material as a measurement of the quantity versus the amount of time or the elution volume it took to come from the column.

Using a calibration curve, each fraction along the chromatogram can have a molecular weight determined for it, and you can produce a relative estimation of the amount of material at each point of the determination. In using that information, you can use an equation to determine Mn and come up with a number.

Q. Mn refers to number average, correct?

A. That is correct.

Q. Is that calculation done with software typically?

A. It can be, but doesn't have to be.

Q. Is it difficult to do that calculation?

* * *

[67]

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Q. (By Mr. Aannestad) What do you mean when you say doesn't -- Gaussian distribution doesn't apply to copolymer-1 unless you produce a peak?

(Court reporter interruption.)

Q. (By Mr. Aannestad) Gaussian distribution doesn't apply to copolymer-1 unless you produce a peak?

A. A Gaussian distribution applies to a curve. Copolymer-1 is not a curve.

Q. Okay. I see. So if you -- well, I think we've -- we've covered that.

Can you look at paragraph 42, please? Can you please read the second sentence for the record?

A. "An easier and more common method, however, is to correlate the elution volume or retention time on the chromatogram to molecular weight through standards that have known molecular weights."

Q. Do you know what the molecular weights are of the standards used in the patents for the SEC?

A. No, I don't. They were not mentioned in the patents.

Q. Turn the page to page twenty, please. You have a polymer distribution curve there, correct?

A. Correct.

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[75]

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A. You construct the calibration curve using a variety of standards. Calibration curve is related to elution volume. And the elution volume on the chromatogram that coincides with that coincides with that molecular weight.

Q. Do you need the calibration curve to determine molecular weight?

A. That's just one way of doing it. There are other ways.

Q. If you're doing size exclusion chromatography, do you need calibration curve to determine molecular weight?

A. Not absolutely.

Q. Okay. What else could you do? A. You could do mass spectrometry on the fractions.

[76]

Q. If you're using a calibration curve to determine molecular weight, do you need to know what standards are used?

MS. HOLLAND: Objection to form, vague and ambiguous.

A. I don't need to know what standards you use. I just need to know that standards were used and the curve was constructed.

Q. (By Mr. Aannestad) Do you need to know what the weights were of those standards?

A. They are given in the curve.

Q. If if you have the curve, correct?

A. Correct.

Q. If you don't have the curve, then they're not given, correct?

A. I believe so.

Q. Looking at page twenty still, do you see the heading "IX. Claim Construction"?

A. Yes.

Q. Does this begin the portion of your declaration where you state your opinions on claim construction?

A. This begins the portion that I state my opinions on claim construction.

Q. Please turn to paragraph 54. Do you see in that paragraph you talk about "the term 'molecular weight,' unmodified by terms that would imply an average molecular weight"?

A. I do.

Q. What terms imply an average molecular weight?

MS. HOLLAND: Objection to form.

[77]

A. Something that indicates that there is more than a single species present.

Q. (By Mr. Aannestad) Can you please read the first sentence of paragraph 55 for the record?

A. "The person of skill in the art would have understood that because copolymer-1 is a mixture of polypeptides that are non-uniform with respect to molecular weight, it cannot have 'a'" -- in parentheses -- "molecular weight."

Q. What do you mean by that?

A. Or in quotations, excuse me.

Q. What do you mean by that?

A. Well, I'll refer to my opinion above on molecular weight, that when referring to an individual species, the ordinary meaning of molecular weight is "the sum of the atomic weights of the atoms making up a molecule."

In a mixture you have more than a single molecular weight species, so that you cannot characterize the mixture by adding up the sum of the atomic weights of the species. Thus, it cannot have a molecular weight defined in terms of paragraph 54.

Q. Turn to paragraph 57. What do you mean by "an appropriately calibrated suitable gel filtration column"?

[78]

A. It means that you determine a molecular weight at the peak of the chromatogram. You can

use a calibrated gel filtration column that has produced a calibration curve.

Q. What do you mean by "appropriately calibrated"?

A. It needs to be done correctly.

Q. And how would one do that correctly for copolymer-1?

A. One would run suitable standards, construct a calibration curve, and relate the elution volume of copolymer-1 from a chromatogram to the calibration curve.

Q. What are suitable standards for copolymer-1?

A. My opinion that suitable standards for copolymer-1 in a person skilled in the art would employ standards that had the same hydrodynamic properties as copolymer-1.

Q. Are there commercially-available suitable standards for copolymer-1?

MS. HOLLAND: I'm sorry. Can you put a [79] time frame on that?

Q. (By Mr. Aannestad) Let's start currently.

A. I am not aware of all of the standards that are available in the world, but I do not recall that there are commercial copolymer-1 standards available.

Q. There are not suitable commercial copolymer-1 standards available, is that your testimony?

A. "Suitable" is a matter of judgment. I would have to consider the specific standard and tell you whether I think it's suitable or not.

Q. Sitting here today, you're not aware of any commercially available standards for copolymer-1; is that correct?

A. I don't know right now where I can go and buy it.

Q. If you can't buy it, how would you obtain suitable standard for copolymer-1?

A. There are several ways. I could make it by synthesizing it. I believe that I could also fractionate copolymer-1 to a very, very high resolution and determine the molecular weight of that fraction to a certain tolerance and use it as a standard.

* * *

[90]

* * *

weight.

Q. Would you please read the first two sentences of paragraph 61 for the record?

A. "Example 1 of the specification states that the molecular weight distribution of copolymer-1 was determined on a calibrated gel filtration column, specifically a Superose 12 column, using a UVIKON spectrophotometer."

Q. Then there's a citation, correct, to that?

A. "See the '808 Patent, col. 3, lines 3-8."

Q. Please read the next sentence as well.

A. "As such, a person of skill in the art would have understood that the method of determining

molecular weight distribution was size exclusion chromatography, and that a calibration curve was generated to correlate molecular weight with elution volume or retention time."

Q. So in your opinion, the inventors generated a calibration curve, correct?

A. Yes, I believe so.

Q. And that calibration curve is not described in the patents, correct?

A. I do not recall that it is.

Q. When you publish your papers on – publish [91] papers that utilize SEC and calibration curves, do you prove the standards?

A. In general I do.

Q. Are you aware of any instances where you did not?

A. Sitting here right now, I am not aware. I'd have to review all the papers to be able to answer that question.

Q. Please read the sentence beginning "Peak molecular weight can be obtained directly."

A. "Peak molecular weight can be obtained directly from the chromatogram and the calibration curve, but further data manipulation and calculation is needed to calculate either the weight average molecular weight or the number average molecular weight."

Q. You rely on figures one and two of the patents for your opinion, correct?

A. Figures one and two are the only figures that are provided in the patents.

Q. And you rely on those, correct?

A. I -- for this statement and my opinion, I rely on my knowledge that that's the appropriate way to do it. Figures one and two are just examples of

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[94]

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Q. Would you publish a paper using the term "average molecular weight" for a polymer, meaning peak molecular weight, without expressly telling the reader that?

A. Possibly. Because in my opinion it's implied.

Q. Why is it implied?

A. Because evidence for other usages are not provided.

Q. So in your opinion, is peak molecular weight the default meaning of average molecular weight if nothing else is stated?

A. In my opinion as far as the patents-in-suit are concerned, the meaning of average molecular weight is peak molecular weight.

Q. That's not my question. My question is: Is peak molecular weight the default meaning to a person of skill in the art of the term, quote, average molecular weight?

MS. HOLLAND: Objection to form, ambiguous.

A. As I said in the declaration, average molecular weight can refer to several different types of average molecular weight.

Q. (By Mr. Aannestad) Is any one of those [95] types a default meaning to a person of skill in the art?

A. I would not term it that way.

Q. Is there anything in the patents themselves that expressly state that average molecular weight means peak molecular weight?

A. I do not recall that there is, but I would have to go through the patents again to be able to answer that question completely. But I do know that it's expressed in the prosecution.

Q. Is peak molecular weight the ordinary meaning for average molecular weight?

A. As I stated before and in the declaration, there are several different meanings for average molecular weight. I do not know what you mean by ordinary.

Q. Looking at paragraph 62, do you see your statement, "The peaks of the curves are close to those numbers"?

A. I do.

Q. What do you mean by "close"?

A. I mean the common usage of the word "close," that they are similar. They're in the vicinity of.

[96]

Q. Later on you state that a person of ordinary skill in the art -- let me correct that. "A person of

skill in the art would have understood that the peak positions on the curves are within a margin of error of the corresponding identified average molecular weights." Do you see that?

A. I do.

Q. What margin of error are you referring to?

A. I don't believe I'm referring to a specific margin of error. I am referring to a margin of error.

Q. Any margin of error, is that what you're referring to?

A. Not any. A margin of error.

Q. What margin of error do you mean?

A. The margin of error that exists.

Q. And what -- what margin exists here?

A. Well, as stated in the declaration, 7.7 compared to 6.8. Twelve compared to eleven.

Q. And what is stated?

A. That's what's stated.

Q. What is stated about the margin of error?

A. There's no explicit statement that what the margin of error is, but it's my opinion that when you compare two values that are different, there is a [97] margin of error.

Q. Isn't any error a margin of error?

A. Any error can be, but it may not refer to this particular error.

Q. Well, if all you're saying is a margin of error, isn't fifty percent error a margin of error?

A. Fifty percent error -¬MS. HOLLAND: Objection -- sorry, objection to form. You can answer.

A. Fifty percent error is a margin of error.

Q. (By Mr. Aannestad) Hundred percent error is a margin of error?

A. It is a margin of error.

Q. Two hundred percent error is a margin of error?

A. Sure.

Q. Two thousand percent error is a margin of error?

MS. HOLLAND: Gen — I assume all these questions mean generally?

A. Yeah. A margin of error is a margin of error.

Q. (By Mr. Aannestad) Why didn't you state a particular margin of error here?

[98]

A. Didn't feel that it was necessary.

Q. Why not?

A. Because my opinion was that there was a margin of error.

Q. Did the lawyers suggest to you using a margin of error without specifying the particular margin of error?

A. I want to make it very clear that these are my opinions. These are not the lawyers' opinions.

Q. Okay.

A. I conferred with the lawyers and gave them my opinions. Somebody put words on a piece of paper. I reviewed it very, very carefully and agreed that they were my opinions.

Q. So you stand by all of these opinions?

A. I do.

Q. Would you use the phrase "a margin of error" to define your margin of error in a publication you're an author on?

A. I may very well use the expression that there is a margin of error. I may then or may not define what that margin of error is.

Q. You would publish a paper without stating what the margin of error is?

[99]

A. It depends the context in which it was used.

Q. In what context would you feel it's not necessary to state what margin of error you're using?

A. For instance, in the discussion section of a paper I could say that the data indicates that there is a margin of error. If that margin of error was listed someplace else in the paper, I don't have to restate it.

Q. Okay. If that margin of error is not listed somewhere else in the paper, would you need to state it?

A. If I wanted to make a point about it.

Q. Then yes?

A. I can say that there is a margin of error without needing to state what that margin of error is.

Q. But you need to state what that margin of error is somewhere, correct?

A. Depending upon what point I'm trying to make. If I'm trying to say that that margin of error is important for some particular point that I'm trying to make, then I suppose that I would want to state what it is. But it's not incorrect to say that there's a margin of error because, in fact, in [100] everything you do there is a margin of error.

Q. Is the margin of error here in paragraph 62 important?

A. That's a value judgment.

Q. In your opinion, is the margin of error in this paragraph 62 important for what you're trying to say?

A. In my -¬

MS. HOLLAND: Object — sorry, objection to form. Go ahead.

A. In my opinion, there is a margin of error, and by giving the numbers I have said what that margin of error is.

Q. (By Mr. Aannestad) What is the margin of error that you've stated?

A. The margin of error is not stated explicitly, but it can be deduced from the information given.

Q. Is there any objective standard to this margin of error?

A. Can you clarify what you mean by "objective standard"?

Q. Is there any objective basis on which you decided that the -- the differences stated in these [101] peaks are acceptable to you?

A. I did not state whether they were acceptable or not. I simply stated that they existed.

Q. Would you publish a paper using figure one?

MS. HOLLAND: Objection to form.

A. Figure one is not mine. Why would I publish it?

Q. (By Mr. Aannestad) Well, if -- if you --would you publish a paper using figure one as it exists to describe that data without changing the figure at all?

MS. HOLLAND: Objection to form.

A. I mean, figure one is not my figure. I wouldn't publish it. I -- I mean, it's somebody else's property.

Q. (By Mr. Aannestad) Would -- would you publish a figure with the same errors as in figure one?

MS. HOLLAND: Objection to form. You can answer.

A. Possibly. Depends upon my reason for publishing it and the point that I was trying to make.

Q. (By Mr. Aannestad) What do you mean when you say in paragraph 62 "which would support the [102] assumption that the numbers in the legend were peak molecular weights"?

A. What line is that?

Q. It's in the third sentence of paragraph 62.

A. I do not see those words.

Q. "The peaks of the curves are close tc the those numbers."

A. That's the --

Q. I was omitting the citation.

A. "The peaks of the curves are close to those numbers, which would support the assumption that the numbers in the legend were peak molecular weights."

Q. What do you mean that it's an assumption?

A. Well, the figure gives values for average molecular weights, and since calculations or descriptions of other types of molecular weights were not given, and the only thing that was given was a peak, then my opinion is appropriate to assume that the legend refers to peak molecular weights.

Q. It's necessary to assume peak molecular weights because it's not expressly stated, correct?

A. The peak molecular weight is the only information that's provided.

Q. Does figure one expressly state that [103] average molecular weight means peak molecular weight?

A. No. It simply expresses average molecular weight.

Q. In your conclusion, that average molecular weight means peak molecular weight is based on your assumption, correct?

A. It's based on more than that.

Q. What else is it based on?

A. It's based on the fact that the -- as stated in my declaration, that the prosecution states that it is so.

Q. Other than the prosecution, is there anything in the patents that supports your opinion?

MS. HOLLAND: Objection, asked and answered. We've been talking about it for the last fifteen minutes.

A. I believe I have answered that.

Q. (By Mr. Aannestad) Other than the prosecution, is there anything else in the patents that supports your opinion?

A. Yes. A peak is provided on a scale with molecular weight.

Q. So based on what you have discussed in the patents, it's your assumption that average molecular [104] weight means peak molecular weight?

A. It is my opinion that average molecular weight refers to peak molecular weight.

Q. Based on an assumption?

A. Based upon my knowledge, based upon my experience.

Q. Based upon the lack of a discussion of calculating number average and weight average molecular weight, correct?

A. That, plus the fact that a peak is provided on molecular weight scale.

Q. Is there anything else in the patents themselves that you rely on for your opinion that a person of skill in the art would assume that average molecular weight means peak molecular weight?

A. Without reading the patents in their entirety, I do not recall that there is. But it is my opinion that that is correct.

Q. You state in this paragraph 62 "that the process of transferring the data from the chromatogram would likely cause the peak on each curve to shift slightly." Why is that?

A. Because any process that deals with manipulating data has an inherent error associated

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[113]

* * *

estimate it.

Q. Why isn't it correct to do so?

A. Because it should be calculated from the original chromatogram.

Q. Why is that?

A. Because the original chromatogram holds the primary datA.

Q. And is that more accurate?

A. I believe it would be. It's likely that it would be.

Q. Why are you willing to calculate the peak molecular weight as the average molecular weight from figure one if you're not willing to calculate the number average molecular weight?

A. I didn't say I'm not willing to.

MS. HOLLAND: Objection -- I'm sorry.

Objection to form, mischaracterized the previous testimony.

Q. (By Mr. Aannestad) Why would you not?

A. I didn't say I wasn't willing to.

Q. Well, why would you not do that in your opinion?

A. Because I think you -- the correct way to do it is from the primary datA.

[114]

Q. And would the correct way to calculate the peak be from the primary data?

A. I believe that is -- the average molecular weights which are provided in the legend are from the primary data, and that the differences that we have discussed come about from the transformation to this form.

Q. But you don't have any specific basis to know that there was a difference caused by the transformation?

A. I do not have the primary datA.

Q. And you haven't asked for the primary data?

A. No, I have not.

(WHEREIN, Exhibit DDX 57 was marked for identification by the Court Reporter.)

Q. (By Mr. Aannestad) You've been handed Exhibit DDX 57. Can you please mark the apex of those curves?

A. I can mark what I believe to be the apex by visual inspection.

Q. Okay. I have a magnifying glass if that would be helpful.

A. I mean, I would point out that this is not what I was asked to do to base my opinion on.

[115]

Q. What were you asked to do?

A. I was asked to do it based upon this.

Q. Okay. Does DDX 57 look similar to figure one of the patent?

A. One could say that it looks similar, but there are differences.

Q. Okay. Could you please mark the apex of those curves?

A. [Witness indicates.]

Q. Could I please see your copy of DDX 57? And is this approximately where you marked the apex on figure one of the '808 patent in rendering your opinions?

A. I don't have that in front of me, so I don't know.

Q. Well, you have the '808 patent in front of you, correct?

A. Yeah. But I -- but it doesn't have a marking on it.

Q. Okay.

(WHEREIN, Exhibit DDX 58 was marked for identification by the Court Reporter.)

Q. (By Mr. Aannestad) Can you please mark the apex on Exhibit 58 -- DDX 58 that you've just been [116] handed in the same spot that you marked them in DDX 57?

A. [Witness indicates.]

Q. Can I see Exhibits DDX 57 and 58, please? Looking at the twelve kilodalton line on DDX 58, where does your marking of the peak measure on the X axis in molecular weight?

A. Well, first of all, there is not a twelve kilodalton line.

Q. Curve?

A. There is no designation of twelve kilodaltons there.

Q. Okay.

A. So I would have to estimate it visually.

Q. Is there a curve that corresponds to -¬

A. Are you referring to the twelve average molecular weight curve?

Q. Correct. In your opinion?

A. Okay. And the question –

Q. Yeah, that curve.

A. The question is?

Q. Yeah, where is the apex of that curve as marked by you on DDX 58?

A. It's approximately at 10,000.

[117]

Q. Is it slightly below 10,000?

A. Could be. It's very close.

Q. Does that change your opinion regarding the peak being at 11,000?

A. No, because I've done this by hand and visual inspection twice. There is inherent error in it.

Q. There's an even greater margin of error than previously?

A. Perhaps. But if I do it again there might be less.

MR. AANNESTAD: I think we need to change tapes.

VIDEOGRAPHER: We're going off the record at 11:47 A.m.

(WHEREIN, a recess was taken.)
VIDEOGRAPHER: We're back on the record on tape three at 12:03 p.m.

Q. (By Mr. Aannestad) Dr. Grant, looking at Exhibit DDX 58, where does your mark on the curve corresponding to the 7.7 molecular weight fall in terms of the X axis?

A. Well, I would have to estimate it based on the fact that that tick does not appear to be [118] accurate. But I would estimate -- without a ruler, it's difficult to appreciate that.

Q. Here's a ruler.

A. I estimate it's approximately seven.

Q. Can you do an area under the curve calculation for figure one?

A. Now?

Q. Yeah. Do you know how?

A. No, I do not.

Q. Can't do that sitting here?

A. No. That involves integration of that curve.

Q. Could you do an estimation of the area under the curve?

A. Not a very accurate one.

Q. All right. Could you do a rough one?

A. I would hesitate to do so.

Q. Could you do one using figure [137] DDX -- a rough estimate using figure DDX 58?

A. I think it would take a considerable amount of time, and it's not something that's normally done by hand. It's usually done with computer software.

Q. In your opinion, would the -- should the area under the curve, under each curve of figure one [119] add up to 100 percent of molar -- of total mass?

A. I believe I answered that before when I said that if 100 percent of the mass was considered in the

construction of the figure, it should have been 100 percent.

Q. Is 100 percent of the mass considered in figure one?

A. There's no indication of 100 percent.

Q. You don't know?

A. No.

Q. Nothing in the patent tells you whether it is or not?

A. I'm not exactly sure what you're getting at here, but the -- what the question actually is, but if I understand it correctly, I don't recall that there is.

Q. Assuming that all the mass was considered under the curves in figure one, should that add up to 100 percent?

A. If the curve was constructed correctly and all the data is available, it should be very close. Within the error that's inherent in any process.

Q. Is your answer the same for figure two?

A. Well, figure two does not plot the mass.

[120]

Q. Should the area under the curve figure two add up to approximately 100 percent molar fraction?

A. It should add up to approximately that. You have to appreciate that these are not particularly rigorously-generated curves in my opinion.

Q. You mean figure one and figure two?

A. They were generated to a certain tolerance, which I was not -- I'm not aware of what the tolerance is. I mean ...

Q. I was asking you earlier about the percent difference between your opinion of the peak and the stated average molecular weight in figure one. And I have a more regular calculator for you. Could you please calculate for me the difference between your measurement as stated in your opinion in paragraph 62 for the 7.7 kilodalton curve?

A. Okay. So I'll point out that the molecular weight in the legend to the curve says 7.7. And molecular weight that is stated as being measured is 6.8. So one way of doing it is to take 7.7, subtract 6.8, which is the difference between the two. And as a percentage being a portion of the whole, divide by 7.7, that equals 11.7 percent.

Q. And is another way of doing that to divide [121] that difference by 6.8?

A. Well, I don't think that adequately reflects the -- the error in the weight that was expressed in the legend.

Q. Would that also be a measurement of the differential between where you measured the peak and the statement in the legend?

MS. HOLLAND: Objection to form.

A. Repeat, please.

Q. (By Mr. Aannestad) Would that also be a measurement of the differential between where you measured the peak on that curve and the statement in the legend?

A. The difference between the two is a measure of the differential. If you asked me to compute the percentage error, it has to be based upon the expressed number, not based upon the experimentally-or manually-derived number.

Q. What is the error in your calculation for the twelve kilodalton curve?

A. I'll do it the same way, except it's not -¬there we go. 8.3 percent.

Q. What is the error for the twelve kilodalton curve based on your marking today on DDX 58?

[122]

A. 16.7 percent.

Q. Is that an acceptable margin of error to you?

A. The target margin of error was not mentioned, but I believe that in my opinion to a person skilled in the art for this purpose, that's close enough.

Q. In your opinion, that's close enough for a person of skill in the art to assume the meaning peak molecular weight for the purposes of the patent disclosure?

A. My opinion is as stated in the -- in the declaration. A person of skill in the art would have understood that the peak positions on the curves were within a margin of error with the corresponding identified average molecular weights.

(Court reporter interruption.)

A. Corresponding identified average molecular weights.

Q. (By Mr. Aannestad) Standing alone, if you were only relying on figure one, would that still be your opinion that a person of skill in the art would assume that average molecular weight means peak molecular weight?

[123]

MS. HOLLAND: Ob -- objection. It mischaracterizes previous testimony.

A. I've stated my opinion in the declaration.

Q. (By Mr. Aannestad) Okay. And what I'm asking you is if -- if the only data the person, the hypothetical person of skill in the art had was figure one, not the rest of the patent specification or the prosecution history, in your opinion would that person assume the average molecular weight means peak molecular weight?

A. I believe I already stated that that's what I believe.

Q. On that basis alone?

A. I don't think it's appropriate to ask me to do it on that basis alone because I was asked to review the patents-in-suit and portions of the prosecution. And that's what I based my judgment on.

Q. If all you had was the figure, in your opinion would you reach the same conclusion?

A. If I was asked whether or not the average molecular weight stated in that figure was close enough to the peaks in that figure to indicate a peak molecular weight, I would say yeah, it's probably close enough.

[124]

Q. You would be willing to assume that?

MS. HOLLAND: Objection to form.

A. I believe I just said that.

Q. (By Mr. Aannestad) Looking at your first sentence of paragraph 63, can you please read that sentence for the record?

A. "A person of skill in the art, knowing that there are other average molecular weights that are used to describe polymers, could also have considered the possibility that the term 'average molecular weight' refers to the number average molecular weight Mn or weight average molecular weight Mw."

Q. By "could," do you mean would?

A. No, I mean "could."

Q. So you don't -- in your opinion, a person of skill in the art would not necessarily have considered the other types of ave -- or the -- I'm sorry, would not necessarily have considered average molecular weight or number?

A. Not necessarily.

Q. Please read the next sentence.

A. "However, a person of skill in the art would have understood that, on a molecular weight distribution curve, Mn typically is smaller than Mp."

[125]

Q. How much smaller?

A. Impossible to say.

Q. Well, what's typical?

A. Typical is that it often happens that way.

Q. So it's impossible for you to say how much smaller Mn typically is than Mp?

A. It depends on each specific instance.

Q. Can they be the same?

A. They can be.

Q. Do you know if they're the same in the case of figure one?

A. No, I do not.

Q. They could be the same?

A. Since it's possible for them to be the same, they could be the same.

Q. Please read the next sentence.

A. "Therefore, if the 'average molecular weights' referred to in Figure 1 were Mn, the person of skill would have expected the peak on the curve to have a higher value than 7.7 ... not a lower value."

Q. What do you mean when you say "higher"? How much higher?

A. I do not make a judgment as to how much.

Q. Could be slightly higher?

[126]

A. It could be.

Q. Could be not higher at all?

A. It could be.

Q. Did you try to calculate this?

A. I said before that I think that to do it appropriately you need the original chromatogram, which I do not have.

Q. Did you think about trying to calculate it?

A. I did think about it.

Q. Why didn't you do that?

A. Because I didn't think it would be very accurate. I did a few back-of-the-envelope type things, but I don't think it's an accurate way to do it.

Q. Do you recall what your conclusions were from your back-of-the-envelope calculations?

A. No, I do not.

Q. Do you recall whether they supported your opinion?

A. I believe that they did.

Q. But you don't know?

A. I don't have them in front of me and it was done sometime ago.

Q. So is it your opinion that because the [127] number average molecular weight would have reflected error in the opinion -- or in the figure, a person of ordinary skill in the art would not have relied on the figure to conclude that average molecular weight means number average?

MS. HOLLAND: Objection to form.

A. I've already stated that my opinion is -¬is that the average molecular weights given in the legend do not refer to number average molecular weight.

Q. (By Mr. Aannestad) Why is that?

A. Well, because again, in the declaration it's expressly stated that in the prosecution average molecular weight refers to peak molecular weight. And as I said before, there's no indication that a number average or a weight average molecular weight was calculated based upon what is present in the patents.

Q. Focusing on paragraph 63, can you explain to me why you believe a person with skill in the art would not have understood the average molecular weight to refer to number average?

A. Would not have understood?

Q. Correct.

A. Or would have understood that the number – [128] the -- the average molecular weight does not refer to number average molecular weight?

Q. Correct.

A. Because there's no indication to suggest that it does.

Q. Is there any indication to suggest that it's peak average?

A. Yes, because peaks are presented.

Q. Is your opinion based on the fact that there would be a greater difference between the stated average molecular weight in the legend and where you believe number average might be?

A. These are generalities. I have no way to come up with a quantity for you.

Q. In paragraph 64 where you say the weight average molecular weight would be significantly

larger than the average molecular weights, what did you mean by "significantly larger"?

A. I meant it would be larger, and I made the conclusion that it would be significant.

Q. What was that based on?

A. Based upon what I know about the relation between -- the general relation between number average, peak average, and weight average molecular weight.

[129]

Q. Do you have any way to quantify that?

A. If I had the original chromatogram I could calculate it.

Q. You don't have that, do you?

A. No, I do not.

Q. You didn't ask for that, did you?

A. No, I did not.

Q. Did the lawyers ask you to not calculate mole weight average molecular weight?

MS. HOLLAND: This is -- this is a communication from counsel. I guess if we didn't ask him then there wasn't a communication, so he can answer the question. If we didn't -- can I -- let me read that again.

There's an agreement about communications from counsel, but I believe since this was not a communication that he can answer the question.

MR. AANNESTAD: Okay.

A. The lawyers did not ask me to not calculate the molecular weight.

(Court reporter interruption.)

A. The molecular weight. I'm sorry.

Q. (By Mr. Aannestad) Please read the

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[134]

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A. I don't understand your question.

MS. HOLLAND: I don't — I think it's — I think the question is ambiguous because it -- what's said in paragraph 64 is not inconsistent with what's in the

Q. (By Mr. Aannestad) Well, the '847 patent may not literally have the -¬

MS. HOLLAND: I think that's --

Q. (By Mr. Aannestad) -- quotation average molecular weight, correct? But that phrase in your opinion means -- or the -- the phrase "copolymer-1 having a molecular weight" means average molecular weight, doesn't it?

A. No. I say that copolymer-1 molecular weight means average molecular weight in my declaration.

Q. Uh-huh.

A. And that's what I mean.

Q. Okay. And there is a claim in the '847 patent that has that phrase copolymer-1 having a molecular weight, correct?

A. That's correct.

Q. And that means average molecular weight, doesn't it?

[135]

A. My declaration says what it says, and I do not believe that the '847 patent contains the term "average molecular weight."

Q. But it does contain a term that means average molecular weight, doesn't it?

A. According to my declaration, copolymer-1 having molecular weight means copolymer-1 having an average molecular weight.

Q. So the answer is yes?

A. No, the answer is not yes because average molecular weight does not appear in the '847 patent.

Q. But does a term that means average molecular weight appear in the '847 patent?

A. According to the declaration, it can be construed to be that way.

Q. Does that change your opinion at all?

A. No, it does not.

Q. In your opinion, would a person of skill in the art reviewing the prosecution history of the '847 patent understand that that patent relates to average molecular weights?

A. Within the context of everything that we've said today, I believe that it would. But again, I have not read the '847 patent in some time.

[136]

Q. Is it your understanding that the specification of the '847 patent is any different than the specification of the '808 patent?

A. I believe I said in the declaration that the specifications in all the patents-in-suit were essentially the same.

Q. And looking at pages three and four of Exhibit DDX 59, do you have any basis to believe that that is not an accurate representation of the claims

of the '847 patent?

A. The -- what is stated here?

Q. Correct.

A. Without comparing it directly to what is in the '847 patent, I have no reason to believe that it is or it isn't.

MS. HOLLAND: I'm sorry to interrupt, Anders, but I think the confusion is that I don't know that when you handed this to Dr. Grant he -- he understood where it was coming from and that it was attached t a declaration submitted, so -¬

MR AANNESTAD: Okay.

MS. HOLLAND: -- that might be the confusion.

Q. (By Mr. Aannestad) Exhibit 4 is -- well, DDX —

A. 59.

Q. -- 59 is Exhibit 4 from Teva's lawyer Patrice Jean -¬

A. Uh-huh.

Q. -- compiling all the claims of the patents-in-suit that are asserted.

A. Okay. And I am to take it as fact that it is an adequ -- adequate representation of those claims?

Q. Yes. We can stipulate to that.

A. Okay. And then the question is?

Q. Well, do you -- do you have any -- the last question was: Do you have any basis to believe that those are not accurate for the '847 patent?

A. If you stipulate that they're accurate, why would I have a basis to believe they're not?

Q. Right. And -- and the point of the inquiry was that the claims of the '847 patent include the phrase "copolymer-1 having a molecular weight," correct?

A. I believe so.

Q. And in your mind, that means to a person of ordinary skill in the art copolymer-1 having an [138] average molecular weight, correct?

MS. HOLLAND: I think it's been asked and answered. You can answer again.

A. Well, I will answer again that I believe paragraph 51 -- 55, if I can find it, states that, "A person of skill in the art would have understood that 'copolymer-1 having a molecular weight' means copolymer-1 having an average molecular weight."

Q. (By Mr. Aannestad) Did you have that in mind when you wrote paragraph 64?

A. Yeah, I believe I did.

MS. HOLLAND: When you get to a convenient breaking point, we can take lunch.

Q. (By Mr. Aannestad) Specifically, did you have that in mind when you rendered your opinion in the parenthetical in paragraph 64?

A. In the parenthetical which is?

Q. "Which does not include any claim that recites 'average molecular weight'"?

A. Again, I have to state that I do not believe that the word "average molecular weight" appears in that patent.

Q. But you didn't point out to the Court that that patent includes claims with a term that means [139] average molecular weight, did you?

A. I did in my declaration.

Q. Did you do that in paragraph 64?

A. I didn't believe it was necessary since it's in my declaration.

Q. It was -- it should have been obvious to somebody?

A. It's in the declaration.

MS. HOLLAND: Object to form, argumentative.

MR. AANNESTAD: Okay. Okay. Why don't we take lunch.

MS. HOLLAND: Okay.

VIDEOGRAPHER: We're going off the record at 12:34 p.m.

(WHEREIN, a lunch recess was taken from 12:34 p.m. to 1:24 p.m.)

VIDEOGRAPHER: We're back on the record at 1:24 p.m.

Q. (By Mr. Aannestad) Good afternoon, Dr. Grant.

A. Good afternoon.

Q. Returning to your declaration, paragraph 64. Is it possible that the weight average [140] molecular weight could be the same as the peak molecular weight?

A. That's a little bit more of an intricate question to answer. I don't think that it is, but I don't want to go on record as saying absolutely it's not.

Q. Before lunch we were talking about the statement during prosecution in the '847 patent about average molecular weight meaning weight average molecular weight, correct? Do you recall that discussion?

A. No, we did not, in my recollection.

Q. Okay. Well, we were leading up to that with the '847 patent, I guess. So I'll -- I'll just withdraw that.

Could you please read the sentence that starts, "Although, during the prosecution"?

MS. HOLLAND: I think that's been read into the record already. But go ahead.

A. Okay. "Although, during the prosecution of the '847 patent (which does not include any claim that recites 'average molecular weight'), the

applicants stated that 'kilodalton units implies a weight average molecular weight,' (see the '847 patent prosecution [141] history, 6/26/2002 Amendment (attached as Exhibit J), page 3 [TEV000304498]), a person of skill in the art would have understood that to be a misstatement because kilodalton is the unit for any measurement of molecular weight, not just Mw, and the person of skill would have recognized that Mw would very likely be greater than stated in the Figures based on the information provided in the curves."

Q. (By Mr. Aannestad) So in your opinion during prosecution of the '847 patent, Teva made a misstatement to the PTO?

MS. HOLLAND: Objection to form.

A. That's correct.

Q. (By Mr. Aannestad) What do you mean when you say weight average molecular weight, Mw, would very likely be greater than stated in the figures?

A. As I stated just a few minutes ago, I believe that it is always larger than number average molecular weight, but I don't want to go on record as saying that it -- it could not be under certain circumstances be the same.

Q. Always larger than number average? Okay. And what about its relation to peak molecular weight?

A. Well, in -- let me say that this, of [142] course, depends to a certain extent on the shape of the peak, the curve, and it's difficult to generalize for all curves. But for curves that are in the patent

that we're dealing with, I think that it's a reasonable statement to make.

Q. And what is that based on?

A. It's based on my -- my knowledge, my experience, my reading.

Q. Did you do any calculations?

A. Of what?

Q. Of where weight average would be on the data set represented by figure one?

A. I believe I stated earlier that I did some preliminary -- I think I called them back-of-the-envelope calculations. They were not detailed calculations.

Q. Why didn't you include those calculations in your declaration?

A. Didn't feel that it was necessary to state my opinion.

Q. Would it have been possible to do a more detailed calculation?

A. Again, as I stated before, I think that the correct way to do the calculation is with the original [143] primary data and not with the information in figures one and two. But it would be possible to do a calculation on the figure, but I don't know how accurate it would be.

Q. And because weight average molecular weight in your opinion would be different than the average molecular weight stated in the legend, you conclude that those do not refer to weight average molecular weight?

A. I -- I believe that it is very likely that that is the case, and that's the reason that I do not think the legend refers to weight average molecular weight.

Q. Because they're different?

A. Because they are -- yes, because they are different.

Q. The same with number average molecular weight, because that's different you do not conclude that the average molecular weight refers to number average?

A. Well, I do not rely on that alone. As I stated before, I rely on all of the information that was presented to me to form my opinion, and that's only part of it.

[144]

Q. The other part is the prosecution history?

A. No. The other part is the fact that there is no information regarding any attempt was made to compute number average or weight average.

Q. And there's also no information regarding an express statement of peak molecular weight being the average molecular weight, correct?

A. There is in the prosecution.

Q. But nowhere in the patents?

A. To my recollection, no.

Q. Let's talk about the prosecution. In paragraph 64 you discuss the statement to the PTO that

average molecular weight means weight average molecular weight, correct?

A. No. It states that kilodalton units imply weight average molecular weight.

Q. Okay. And then paragraph 65 discusses the instance in the '539 prosecution where Teva told the patent examiner that average molecular weight means peak molecular weight, correct?

A. I believe that's what it says, yes.

Q. Okay. Are you aware of a third instance where Teva told the PTO that average molecular weight had a third meaning?

* * *

[191]

* * *

A. Well, paragraph 27 actually doesn't really stand on its own. I mean, because it involves information from other paragraphs. But he says because the "molecular weights of copolymers vary depending upon the measurement technique."

Actually, what varies is the number that results from the analysis of the copolymers depending upon the measurement technique. And he claims that that makes them further ambiguous. But I'm not sure that I know what he means by "further ambiguous."

If it's a legal term, I'm not capable of rendering an opinion. But he says earlier that it's a -- a complicated question for such mixtures. I agree that it is a complicated question for mixtures, and if

that's what makes it ambiguous, then I guess that's what he's trying to say. But I just have trouble understanding what he means by that paragraph.

Q. Well, given the -- given a clarification that the molecular weights of copolymers means the -¬the numbers -- as you state, the numbers of the molecular weights vary?

A. Uh-huh.

Q. Do you disagree with that?

MS. HOLLAND: I -- I'm going to object. I [192] think that Dr. Grant just said he didn't understand what the paragraph meant.

Q. (By Mr. Aannestad) You testified actually what varies is the number that results from the analysis of the copolymers depending upon -¬(Court reporter interruption.)

MR. AANNESTAD: If you don't type it I can read it. I'm just reading what you have.

Q. (By Mr. Aannestad) Actually what varies is the number that results from the analysis of the copolymers depending upon the measurement technique?

A. Yes.

MS. HOLLAND: I think — I'm sorry. I think that the -- that Dr. Grant also said he wasn't sure what he meant by "further ambiguous." And clearly that would have to be understood in order to be able to comment on that paragraph.

Q. (By Mr. Aannestad) Well, I'm not -- I'm not asking a general question on the paragraph right now.

A. Well, I mean, the science says that different analytical techniques provide different numbers for polymer mixtures. For instance, I believe that I stated earlier in my declaration, if I can find [193] it, in paragraph 38 of my declaration, "For example, when a sample of a polymer is measured by osmometry, the molecular weight obtained is a number average molecular weight (commonly referred to as 'Mn'), which represents the total weight of the sample divided by the total number of moles of molecules which it contains. On the other hand, when a sample of polymer is measured by MALLS," M-A-L-L-S, "the larger molecules will make a greater contribution to light scattering than an equal amount of smaller ones, and the molecular weight obtained is a weight average molecular weight."

So going back to his statement that because molecule weights of copolymers vary depending upon the measurement technique, which is what I said in my declaration, a condition used, the claims are ambiguous. I don't see how it follows from that that the claims are ambiguous because that is inherent in the techniques.

Q. Because depending on the technique used you might know which average molecular weight is being determined?

A. Certain -- certain techniques because of what is measured, the way they're performed, the [194] physical characteristics of the methodology are

known to produce specific types of average molecular weights. Other techniques can produce one or more.

Q. Such as size exclusion chromatography?

A. Such as size exclusion, yes.

Q. And what about the conditions, would that also vary the numbers of the molecular weights?

MS. HOLLAND: Objection to form.

A. I'm not sure that conditions is the word you want to use. I mean, what I would say is that the composition of the polymers will cause the numbers to vary.

I suppose that it is possible that if you change the condition such as the temperature, the pressure, and things like that, you may well come up with a different number. It is usually common practice that the conditions are stated and it is understood that those conditions must be met for reproducibility.

Q. (By Mr. Aannestad) Is flow rate one of those conditions?

A. It can be.

Q. What about the elution buffer?

A. The elution buffer may have an effect.

[195]

Q. What about the pH?

A. The pH may have an effect.

Q. How about the salt?

A. The salt may have an effect.

Q. The choice of column?

A. The choice of column may have an effect.

Q. What about the packing density?

A. Insofar as the packing density will influence the resolution, it may have an effect.

Q. And the particular standards used would have an effect as well, correct?

(Court reporter interruption.)

Q. (By Mr. Aannestad) And the particular standards would have an effect as well?

MS. HOLLAND: Objection to form.

A. If the column were calibrated correctly, it should produce a reasonable molecular weight.

(Court reporter interruption.)

A. Molecular weight. I'm sorry.

Q. (By Mr. Aannestad) Anything ¬

A. Let me continue here.

Q. Anything else about paragraph I guess 27?

A. No.

Q. Okay.

* * *

[Exhibit 13 to the Declaration of David C. Doyle]

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1. INTRODUCTION

Size exclusion chromatography (SEC), also referred to as gel permeation chromatography (GPC), is a well-recognized technique for the determination of polymer molecular weight distributions. However, it is now recognized that some polymers are much more difficult to analyze by SEC than polystyrene and other linear homopolymers. The topic of this chapter is analysis of these "complex" polymers by both SEC,

and by the closely related method of high-performance liquid chromatography (HPLC).

There have been a number of revolutionary changes in chromatographic technology that have occurred in recent years (1-14). In particular

- Size exclusion chromatography is no longer one simple technique. Many options are available in both how the analysis is conducted and how the data are interpreted.

- Size exclusion chromatography is often now used for analysis of properties other than molecular weight distribution, for example, copolymer composition.

- Microprocessors are now commonly installed in SEC instruments to control conditions and to process data.

- New column technology now permits analyses to be conducted in 20 min rather than 3 h. However, strong reliance is placed upon strict control of chromatographic conditions by microprocessors.

- "Chemometrics," the application of computer implemented mathematics, particularly statistics, in chemistry, is now a major, well-recognized area of research, which is strongly affecting data processing.

- High-performance liquid chromatography, a method traditionally used for small molecule analysis, is now being proposed as an alternative, which can be superior to SEC for polymer analysis in some cases.

Selecting analytical options that provide needed results for complex polymers is a critical need in this

dynamic situation. The objective of this chapter is to assist the analyst in this selection.

In the next section, a brief description of SEC and HPLC is provided. Following this description, polymer properties are reviewed and classified. This provides the basis for defining what is meant by "monodisperse," "polydisperse," and "complex" polymers in an SEC-HPLC context. After these definitions are formulated, a plan for systematically examining the alternative methods is presented.

2. DESCRIPTION OF SEC AND HPLC

Figure 1 shows a schematic of a typical instrument that is used for both SEC and HPLC. The sample is dissolved in a solvent, injected into a flowing stream of the same solvent at the top of the chromatographic columns, and carried through the columns at a constant flow rate. When the instrument is used for SEC, the columns are filled with a porous packing (e.g., porous glass or a cross-linked gel). The smaller molecules in the sample go into and out of more pores in the packing than do the larger molecules and exit later. The fractionation is on the basis of molecular size in solution with the largest molecules leaving the columns first followed by the smaller molecules. Thus polymer exits before monomer, and larger molecules in the polymer exit before the smaller ones. Upon leaving the columns, the sample molecules enter one or more sequentially attached detectors. A typical detector is a fixed wavelength ultraviolet (UV)-visible (vis) spectrophotometer. However, as we discuss later in this chapter, many different detectors may be used.

High-performance liquid chromatography utilizes basically the same instrumentation as SEC. However, HPLC utilizes columns that are intended to encourage adsorption and partition mechanisms. Size exclusion is considered not to be present. Currently there is much debate regarding the actual mechanism of separation. A generalized model allowing for the possibility of simultaneous adsorption, partition, and size exclusion has been published (15). In HPLC, the columns used most frequently employ packing of small porosity with a hydrophobic coating. They are termed "reversed-phase" columns because the packings are less polar than the mobile phase (10). Because of the different mechanistic basis for the separation, the solvents used are usually different than employed in SEC. Binary, ternary, and even quaternary

* * *

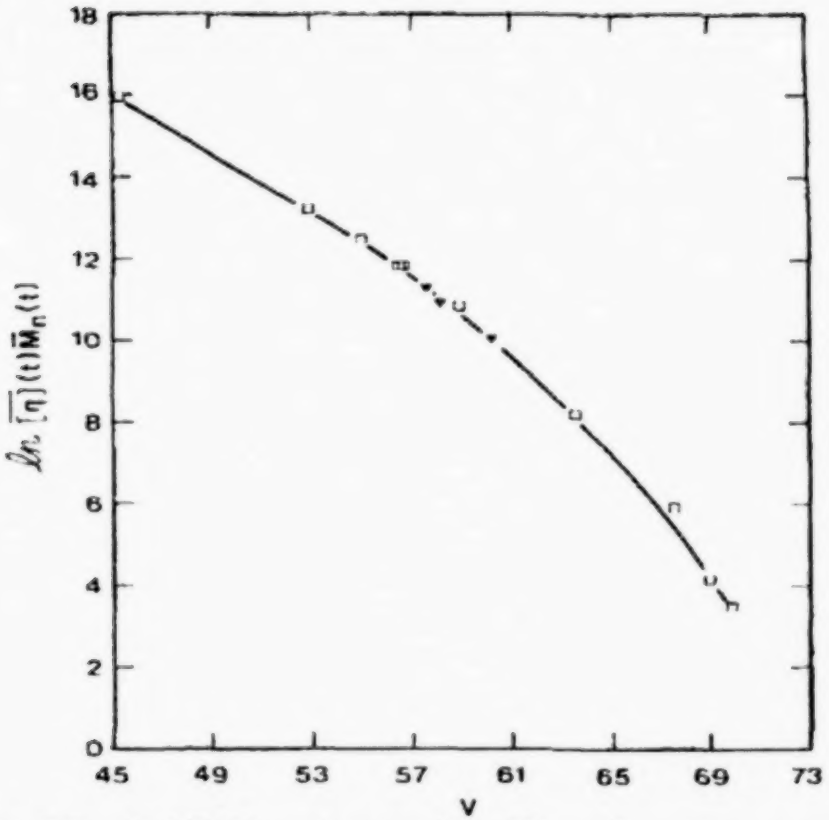


Figure 12. A SEC universal calibration curve: □ polystyrene; ▼ poly(vinyl chloride).

Figure 12 shows an example of a universal calibration curve. Note that both polystyrene samples and poly(vinyl chloride) standards fall on the same curve. If molecular weight is plotted instead of J, two different curves are obtained (Fig. 13). The curve based on molecular size is "universal" because molecular size is the basis of the separation mechanism in SEC. Unlike the curve based upon molecular weight, this universal curve can be determined from narrow fractions of one polymer and used for any other polymer at the same chromatographic conditions. Unfortunately, however, it is the molecular weight versus retention volume curve, which is generally needed. The many methods used to determine it are discussed in Section 7.2.3.

7.2.3. Molecular Weight at Each Retention Volume: SEC Molecular Weight Calibration

Currently, the most widely used method for determining a molecular weight distribution is by interpreting the SEC chromatogram. This requires defining

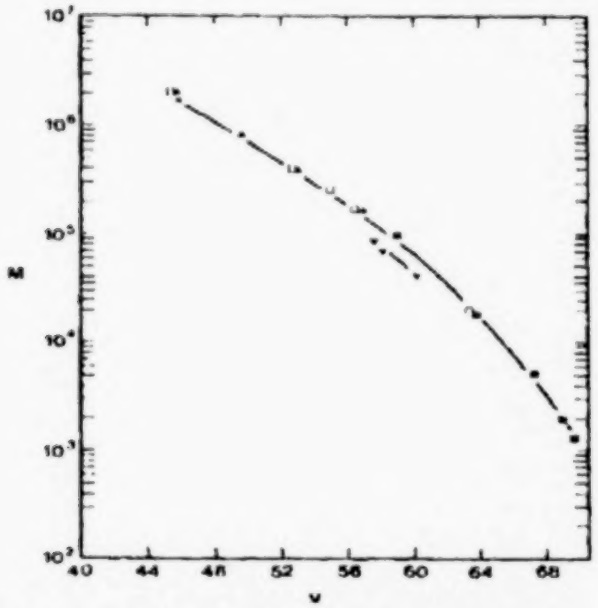


Figure 13. Conventional SEC calibration curves: ▼ poly(vinyl chloride); other points are polystyrene.

the relationship between retention volume in the instrument and molecular weight of the polymer. The mathematical equation used to express this relationship is termed an SEC calibration curve. With it the abscissa of the chromatogram, retention volume of each molecular size present, is converted to molecular weight, and the normalized ordinate, $W_N(v)$, to $W_N(\log M)$ via Eq. 27.

For polymers that have only one distributed property, molecular weight, fractionation by molecular size is synonymous with fractionation by molecular weight. A mathematical relationship

between molecular weight and retention volume (e.g., Eq. 23) then can be expected. However, for complex polymers, many different molecular weights can exist at each retention volume. Conceivably, an infinite number of calibration curves can exist—one for each variety of polymer molecule. Equation 23 becomes a family of calibration curves given by (91)

$$\bar{M}_q(v) = D_{1q}\exp(-D_{2q}v)$$

where local molecular weight averages have replaced the local molecular weight. The subscript $q = 1$ for $\bar{M}_\eta(v)$ and 2 for $\bar{M}_w(v)$. Local intrinsic viscosity can be similarly calibrated and the subscript symbol η then used for q.

There are five primary methods of determining the relationship between molecular weight and retention volume (6, 7, 92).

1. Derivation from a universal calibration curve.

2. Use of monodisperse polymer standards of known molecular weight.

3. Use of polydisperse polymer standards of known molecular weight averages.

4. Use of polydisperse polymer standards of known molecular weight distribution.

5. Use of online detectors that provide a direct measure of molecular weight at each retention volume.

In the following paragraphs, each of these will be described in turn and their applicability to complex polymer commented upon.

7.2.3.1. Derivation from a Universal Calibration Curve. If the polymer can be fractionated so there is only one molecular weight at each retention volume, Eq. 38 can be used to determine M as a function of retention volume. For linear homopolymers, the intrinsic viscosity-molecular weight relationship used is the Mark-Houwink-Sakurada equation (Eq. 10). The calibration curve for the linear homopolymer, denoted by the subscript P, in terms of the universal calibration curve, is

$$M_P(v) = \left[\frac{J(v)}{K_P}\right]^{1/(ap+1)} \tag{41}$$

For complex polymers, the Mark—Houwink-Sakurada equation is not valid. If some other equation is used or if local intrinsic viscosity is measured directly (Sections 6.2.3 and 7.2.3), then from use of Eq. 37 rather than Eq. 38 a plot of $\bar{M}_\eta(v)$ versus v is obtained.

7.2.3.2. Calibration from Monodisperse Polymer Standards. If a series of nearly monodisperse polymer standards are available, each with known molecular weight, then the calibration curve for the polymer represented by these standards can be determined by simply determining the peak retention volume of each standard. In general, such standards are not truly monodisperse. The calibration curve is actually a plot of the peak molecular weight

* * *

[Exhibit 1 to the Declaration of Brian M. Kramer]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC.,	)	
and	)	
YEDA RESEARCH AND DEVELOPMENT CO , LTD ,	)	
Plaintiffs,	)	
vs.	)	Civil Action No. 08 CV 7611 (BSJ)(AJP) ECF Case
SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG	)	
and	)	
MOMENTA PHARMACEUTICALS, INC.,	)	
Defendants.	)	

EXTERNAL COUNSEL ONLY

VIDEOTAPED DEPOSITION OF
GREGORY A. GRANT, PH.D.

TAKEN ON BEHALF OF THE DEFENDANTS SANDOZ, INC. and MOMENTA PHARMACEUTICALS, INC.

FEBRUARY 2, 2010

[36]

peak molecular weight?

A. As I said before, I don't recall ever seeing this before, and I didn't prepare it. So unless you give me sufficient time to study it and make some sort of a judgment, I'm not sure what it means.

Q. Turning to the second page. Do you see at the top of that data set it says peak and then across it says molecular weight 7200?

A. I see that.

Q. The lawyers for Teva have never shared this document with you before, correct?

A. Not --

MR. JAMES: Objection, asked and answered.

A. Not that I recall. Not that I recall.

Q. (By Mr. Aannestad) Since your deposition have you asked for the original data underlying figure one of the '808 patent?

A. No, I haven't.

Q. Why not?

A. I didn't believe that it was relevant to my opinions.

Q. Since your deposition have you calculated the number average molecular weight for the data in [37] figure one?

MR. JAMES: Objection. What -- what does that have to do with this declaration?

MR. AANNESTAD: This declaration is pretty-much about figure one.

MR. JAMES: What does it have to do with the number average of figure one?

MR. AANNESTAD: It has to do with his opinions.

MR. JAMES: That's all you can give me is it has to do with his opinions?

MR. AANNESTAD: I don't need to spend my time explaining it to you. It's obvious this declaration is about figure one.

MR. JAMES: It's not obvious, Anders. You're not entitled to delve into anything you want to today. It's about this declaration. If you can show him where he's talked about number average, I'll let him answer the question.

MR. AANNESTAD: Okay. Well, this is going on your time. It's relevant whether -- he's spoken about that right here.

Q. (By Mr. Aannestad) Paragraph five: Although other types of average molecular weights were [38] known in 1994, including number average weight, weight average molecular weight, z average molecular weight, and viscosity average molecular weight, one would have -- one of ordinary skill in the

art, I'm paraphrasing now, would not have concluded that average molecular weight refers to any of those.

So have you since the time of your other dec -- deposition attempted to calculate number average molecular weight for the data in figure one?

A. I don't think my opinion as expressed in paragraph five needs be based upon a specific calculation of number average molecular weight.

Q. That's not what I'm asking you. I'm asking you have you calculated number average molecular weight of the data in figure one?

MR. JAMES: What do you mean by the data in figure one? Are you asking him if he used the patent or the underlying data?

MR. AANNESTAD: Well, he's already testified he doesn't have the underlying data. Never even asked for it. So the data in figure one, have you attempted to calculate the number average molecular weight from that?

MR. JAMES: You can answer the question.

[39]

A. I believe in my first deposition I said that I did some preliminary calculations of the molecular weight.

Q. (By Mr. Aannestad) You did rough back-of-the-envelope type of calculations?

A. I believe that's what I said, yes.

Q. You didn't keep those, right?

A. No.

Q. Do you recall the methodology you used for that calculation?

A. Not specifically. I mean, at that time I think I looked at different aspects just trying to gain a qualitative appreciation.

Q. Qualitative, not quantitative?

A. Well, I mean, there was some numbers involved that I was just trying to get a feel for the figure mainly.

Q. Just a rough calculation?

A. At that time, yes.

Q. Since that time have you tried to do a detailed calculation?

A. Since what time?

Q. Since the time you did the rough calculation.

[40]

A. How is that question relative to the time of the deposition?

Q. I don't understand your question, and I'm not here to answer questions.

A. Well, I'm -- I'm trying to understand the time frame that you're trying to ask me the question about.

Q. I think we can simplify it. At any time did you try to do a detailed calculation?

MR. JAMES: Objection to the form.

A. At a time after the deposition, and I don't recall exactly when, I did additional calculations.

Q. (By Mr. Aannestad) What did you determine?

A. Isn't that what's called a work product? Because I don't --

MR. JAMES: Well, I don't know. Maybe we should have a discussion, see what -- what he's talking about. If he's not relying on it for his --for his opinions, then I don't think it's covered by this declaration.

MR. AANNESTAD: Well, I mean, I -- I doubt that it can be work product since he's an expert, but if you need to talk to him.

MR. JAMES: Well, I think that the [41] protective order in this matter has a provision in it that excludes certain kinds of notes and other materials generated by experts. So to the extent that it falls within that provision, then I don't think that you would be entitled to discovery on it. So I think perhaps -- I'm not sure what he's talking about, so I think I'd like to take two minutes and talk to him and see what's talking about.

MR. AANNESTAD: All right. Well, talk to him. And I mean, we'll need to see if you're going to assert privilege over work that he's done in -- in formulating his opinions in this case. Okay.

MR. JAMES: Well, I don't think there's any -- you haven't laid a foundation --

(Court reporter interruption.)

MR. JAMES: You haven't laid a foundation that it's anything relating to his opinions in this case.

MR. AANNESTAD: I -- I think that's obvious.

MR. JAMES: You keep saying that, but I --I don't think it is.

MR. AANNESTAD: If he performed calculations on the number average and weight average [42] after his deposition after that questioning based on what went into his first declaration and everything thereafter, it's clear that that relates to his opinions in this case.

MR. JAMES: I don't.

MR. AANNESTAD: So -- well, you can assert privilege if you want but, you know -- okay.

MR. JAMES: Let me have two minutes to find out what it's about.

VIDEOGRAPHER: We're going off the record at 9:23 a.m.

(WHEREIN, a recess was taken.)

VIDEOGRAPHER: We're back on the record at 9:33 a.m.

MR. JAMES: He can answer your question.

A. Could you please repeat your question?

Q. (By Mr. Aannestad) Since your deposition have you calculated the number average molecular weight based on figure one?

A. Yes, I have.

Q. What was the result of that calculation?

A. I don't recall the exact number, but it was consistent with my opinion.

Q. What do you mean by that?

[43]

A. I mean that the opinions that I originally expressed were not changed by my calculation.

Q. Do you have any recollection of what the result of your calculation was?

A. If I had to speculate on what it was it was probably in the range of 55, 5600.

Q. You didn't keep your records from that calculation?

A. Oh, I have the calculation.

Q. You do?

A. Yes.

MR. AANNESTAD: Can we get a copy of that?

MR. JAMES: Yes, to the extent that I have it, if we can find it. I assume -- I assume we can. He says he has it. So assuming we can find it, I'll produce it to you.

Q. (By Mr. Aannestad) Did you do the calculation for weight average molecular weight?

A. Yes, I did.

Q. And what was the result of that?

A. Again, I don't recall exactly, but if I had to estimate what it was, I think it was probably around 83 to 8500.

Q. Do you still have a copy of that?

[44]

A. Yes, I do.

MR. AANNESTAD: We'd like to get a copy of that as well.

Q. (By Mr. Aannestad) Did you do any other calculations based on the data in the patent?

A. I think that that's the only thing that I did.

Q. Have you ever done an area under the curve analysis for figure one?

A. Not -- not -- not a direct area under the curve analysis, no.

Q. What have you done?

A. I have used commonly accepted and proven procedures from the literature for calculating the number average and the weight average from the data.

Q. Have you calculated the area under the curve for figure one?

MR. JAMES: Objection, asked and answered.

A. Yeah, I think I said that I haven't calculated the areas.

Q. (By Mr. Aannestad) Turning to paragraph nineteen of your declaration. Well, before we do that, is what you're referring to with the area under the curve the same calculations you did for weight copolymer-1?

* * *

[71]

* * *

A. As far as I can recall, I have never spoken to any scientist that I knew was employed by Teva.

Q. You state: The person having ordinary skill in the art would have understood that they could use fractions of copolymer-1 that had determined molecular weight values at standards -- as standards. What do you mean by "determined molecular weight values"? What methods?

A. Your question is asking me what methods you would use to determine the molecular weight values?

Q. Yeah. What are you referring to there when you say that -- that you could use co -- fractions of the copolymer-1 with determined molecular weight values?

A. I'm saying that you can use fractions of copolymer-1 that you have determined the molecular weight of.

Q. Have you ever done that?

A. For copolymer-1 specifically?

Q. Correct.

A. No, I haven't.

Q. Have you ever developed a noncommercial standard?

[72]

A. My -- my research does not involve development.

Q. So your answer is you've never developed a noncommercial standard?

A. No, I don't think so I have -- think that I have.

Q. You've only used commercially available standards, correct?

A. That's not entirely correct. I have used some standards that I have generated myself.

Q. Okay. Which ones?

A. I don't recall specifically.

Q. When did you do that?

A. I don't recall that either. I've been doing this for forty years. I can't give you specifics.

Q. So you don't recall any details of ever developing your own noncommercial standard?

A. I wouldn't describe it as developing. I have obtained standards in the laboratory that I didn't buy commercially and that I've used.

Q. And when you state here that you could use -- a person could use fractions of copolymer-1 that had determined molecular weight values at [73] standards, what do you mean by determined molecular weight values? In what techniques?

A. I mean that you -- you would -- you would take these fractions that you have obtained and you would determine what their molecular weights were. I can't speak for other people. I suppose that there are several or -- several different techniques that you could use.

Q. What techniques did you have in mind when rendering this opinion?

A. Well, I think that the technique that I would use to do this would be mass spectrometry.

Q. Are there other techniques that could be used?

A. Yeah, there might be other techniques, but they wouldn't be ones that I would choose as my primary technique.

Q. Okay. Could you use SEC-MALLS?

A. You could attempt to do it, but I -- in this case I -- I -- I wouldn't rely on SEC-MALLS.

Q. Why not?

A. Because when you're.dealing with mixtures, SEC-MALLS basically produce what is a weight average molecular weight, and I do not think that that's [74] appropriate for this purpose.

Q. And if different techniques were used for the determination of the molecular weight of the copolymer-1 intended to use as a standard, would you get different molecular weight and values?

MR. JAMES: Objection to the form of the question, vague and ambiguous.

A. Well, I don't think that I would use different techniques. I think I would use my primary choice, and I think that it would provide reliable values.

Q (By Mr. Aannestad) Well, when you say SEC-MALLS would not be appropriate, what would be the result? Would you get an incorrect value?

A. As I just stated, SEC-MALLS would give you a weight average molecular weight, and I do not think that it would be appropriate to use that molecular weight in determining a peak average molecular weight.

Q. Are you -- are you aware of whether Teva used SEC-MALLS to determine the molecular weight of its copolymer-1 standards?

A. I don't know if they did.

Q. If Teva did use SEC-MALLS to determine the molecular weight of its copolymer-1 standards, you use

* * *

[83]

* * *

molecular weight of those standards was determined using SEC-MALLS, is that information that would be relevant to a person of ordinary skill in the art trying to reproduce the molecular weight –

MR. JAMES: Objection to the form -- sorry.

Q. (By Mr. Aannestad) -- the molecular weights in the patents?

MR. JAMES: Objection to the form of the question.

A. Well, getting back to the -- excuse me --the context of the patent, I mean, I have no idea really if that procedure was used to produce what's in the patents.

Q. (By Mr. Aannestad) Well, I will represent to you that it was, and as an expert you're allowed to assume that as a hypothetical. So either way we're good to go. So assuming those facts, copolymer-1 markers whose molecular weights were determined by SEC-MALLS, would that be relevant to a person of skill in the art trying to reproduce the molecular

weights for their own copolymer-1 based on these patents?

MR. JAMES: Objection to the form of the question, lacks foundation, in -- incomplete hypothetical.

[84]

A. Well, I think a person skilled in the art could figure out how to determine the molecular weights appropriately. And whether or not I assume if somebody used one procedure or another to determine molecular weights, I would also have to assume that they did it correctly to the point that whatever molecular weight that they determined was a reasonable estimate of the molecular weight that1s in the patents.

Q. (By Mr. Aannestad) So that -- your opinion is based on the assumption that whoever did the molecular weight determinations in the patents did it right?

A. My opinion is that a person in the art would know how to do it right. I mean, you know, I said before, and let me just say it again, that even though SEC-MALLS gives weight average molecular weight, it also depends upon what the nature of the standard is that you're --you're using because if the distribution becomes smaller and smaller and smaller, weight average becomes much closer and closer and closer to peak average, and it could come to the point where the difference is small enough that it really hasn't got a substantial effect on the molecular [85] weights that are determined.

Q. Is another way of stating your opinion that the molecular weight would be determined with a suitably calibrated appropriate gel filtration column, that it would be determined with the right ' calibrated -- the right calibration? And basically, by the term "suitably" you mean somebody did it right; isn't that right?

A. Yeah, I guess so. Yeah.

Q. Turning to paragraph 22, you state --this is of your declaration -- "The person of ordinary skill in the art would also have known to treat the samples and standards identically." Why would they treat them identically?

A. I mean, this is just basic science. I mean, this is like chemistry 101 or biochemistry 101. You're taught that that's the appropriate way to do it and that's what you're supposed to do. I mean, you learn that from a very early stage. There is absolutely no reason unless you purposefully wanted to make a mistake that you would do it differently.

Q. Because you could get different results if you did it differently?

A. No, because you know that that's the

* * *

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs/Counterclaim-Defendants,* v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., *Defendants/Counterclaim-Plaintiffs.*	Civil Action No. 09-CV-8824 (BSJ) (AJP)

DECLARATION OF CHANG RYU, Ph.D.

1. I have been retained by Perkins Coie LLP to provide my opinions as an expert witness on behalf of Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (collectively, "Plaintiffs") regarding certain issues that pertain to U.S. Patents Nos. 5,800,808 ("the '808 patent"), 5,981,589 (the

'589 patent"), 6,048,898 ("the'898 patent"), 6,054,430 ("the '430 patent"), 6,342,476 ("the '476 patent"), 6,362,161 ("the '161 patent"), 6,620,847 ("the '847 patent"), 6,939,539 ("the '539 patent"), and 7,199,098 ("the '098 patent"). I will refer to these patents collectively as "the Teva patents" My fees for services as an expert witness in this litigation are $350 per hour. My compensation is not dependent in any way upon the opinions formed or the outcome of this litigation. In the last five years, I have not testified at a deposition or trial, and the materials I considered in preparing the statements below included the patents in suit, U.S. Patent No. 3,849,550, the prosecution histories of the patents in suit with emphasis on the portions mentioned below, Teitelbaum, D., et al., Eur. J. Immunol. 1971. 1: 242-248, Sela, M., et al., Biochem. J. 1962 and Yphantis, D. A., Biochemistry 1964. 3:297.

I. EDUCATION AND EXPERIENCE

2. In 1990, I received my bachelor of science (BS) in Chemical Technology from the Seoul National University (SNU) in Korea, and then my Masters of Science (MS) in 1992 also from Seoul National University in Chemical Technology conducting research projects on polymer chemistry. My CV is attached at Exhibit 1.

3. After receiving my BS and MS from SNU, from 1992-1993, I served as a research scientist at the Korea Institute of Science and Technology, performing polymer synthesis and polymer characterization using analytical tools, including gel permeation chromatography (GPC). In 1993, I started my graduate studies at the University of

Minnesota in the Chemical Engineering program, where I received my Ph.D. specializing in structure property relationship of block copolymers. The title of my PhD thesis is "Structure and Dynamics of Block Copolymer Melts and Solutions." GPC was routinely used to check the molecular weight distribution before and after thermal analysis of block copolymers. For two years after receiving my Ph.D. (1998-2000), I worked as postdoctoral researcher in Materials Research Laboratory in University of California at Santa Barbara working on research projects on polymer synthesis and characterization, which includes the GPC analysis of the block copolymers that I have synthesized using anionic polymerization techniques.

4. I am currently an Associate Professor in the Department of Chemistry and Chemical Biology at the Rensselaer Polytechnic Institute (RPI) in Troy, New York. I am also a faculty member of New York State Center for Polymer Synthesis and National Science Foundation Nanoscale Science and Engineering Center. I started my tenure-track faculty position at RPI in November, 2000, as an Assistant Professor and was promoted to the Associate Professor with tenure in August, 2006.

5. For the last twenty years, my research has utilized gel permeation chromatography (GPC) for the analysis of synthetic homopolymers and copolymers that have polydisperse molecular weight distributions. As soon as I started my faculty position at RPI in 2000, the development of polymer analysis and separation techniques using high performance liquid chromatography (HPLC), including GPC, has been my main focus to advance

our knowledge in characterizing the molecular weight distribution of various homopolymers and copolymers that have a wide range of polydispersity in molecular weight distribution. In my research laboratory at RPI, there are in-house built (i.e. "home-made") GPC/HPLC instruments in addition to commercially available GPC instruments. Over the last several years, my research group has constructed and used home-made GPC instruments to operate and acquire/analyze GPC chromatography data using simple spread sheet software (without using commercial software). It is one of my educational missions to train my graduate students with skills to build up and analyze GPC instruments and to enhance their ability to understand the GPC data and compare their calculation results with those from the commercially available software. We are also working on using more than one detector for the analysis of copolymers, and home-made instrumentation skills in my research group have proved to be useful for the versatile and complicated analysis of polydisperse copolymers.

6. I have published numerous papers in various scientific journals. I have also co-authored several articles, including the article titled "Interaction-Controlled HPLC for Block Copolymer Analysis and Separation" published in the Journal of American Chemical Society in 2004.

7. For the past 5 years I have given the invited seminar entitled "Polymer HPLC Beyond SEC" to address the importance of utilizing polymer HPLC in characterizing copolymers at numerous universities in the United States and abroad.

8. I received the National Science Foundation (NSF) CAREER award (2005 - 2010) for Polymer Adsorpotion and Transport in Nanopores, which funded research projects in my laboratory focused on developing polymer HPLC techniques including GPC and elucidating the fundamental phenomena governing HPLC separations.

9. Through nearly a ten year tenure as an academic faculty member at RPI, I have taught numerous graduate-level and undergraduate-level courses that cover the core chemistry subjects that relate to Analytical, Physical or Polymer Chemistry. I taught an undergraduate course entitled "Modern Techniques in Chemistry," to cover the fundamental principles and experimental chemical analysis techniques, which include the high performance liquid chromatography (HPLC) techniques, and other chromatography techniques, such as gel permeation chromatography. I have also taught "Introduction to Polymer Chemistry," which includes extensive coverage of molecular weight characterization. I additionally designed the graduate level course on polymer separation entitled, "Polymer Separation and HPLC", which mainly covers polymer HPLC techniques. For the past 5 years I have given numerous invited seminars at Universities in the US and abroad entitled "Polymer HPLC Beyond SEC" to address the importance of utilizing polymer HPLC in characterizing copolymers.

10. I am a member of the American Chemical Society in the divisions of PMSE (polymer materials science engineering) and POLY (polymer chemistry). I am also a member of the American Physical Society, Polymer Physics Division. I am currently

the principal investigator for the National Science Foundation (NSF) program entitled Partnership for International Research and Education (PIRE): POLYMER Education and Research Partnership between US and Korea (NSF Award Number 0730243), where I promote the usage of polymer HPLC techniques for characterizing copolymers.

11. I serve on various NSF review panels and review submissions for publication.

12. I serve as a guest editor for the Journal of Polymer Science, Polymer Physics edition in 2007. I am also a reviewer for numerous peer-reviewed journals such as the Journal of the American Chemistry Society, Macromolecules, Journal of Polymer Science, Polymer and Langmuir.

13. I have been asked to provide opinions as to what a person of ordinary skill in the art as of the 1994 timeframe would understand the various terms described in the sections below.

II. LEVEL OF ORDINARY SKILL IN THE ART

14. I have been asked to use the following definition of a person of ordinary skill in the art in 1994 for my opinions on the issues discussed in this declaration:

> The person of ordinary skill in the art of the patents in suit would have an advanced degree or equivalent in a chemical or biological discipline, and significant experience in the synthesis or characterization of polymers, including proteins, synthetic peptides and polydisperse mixtures, as well as experience in the determination of the

molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained.

15. I have been asked to review a number of claims of the Teva patents relating to copolymer-1 having a defined average molecular weight or molecular weight and offer my opinions below. Given my understanding of copolymer-1 and how one in 1994 would determine its average molecular weight, the above definition of a person of ordinary skill appears to be consistent with the subject matter of the claims that recite copolymer-1 having a defined average molecular weight or molecular weight.

III. BACKGROUND ON MOLECULAR WEIGHT ANALYSIS OF COPOLYMERS

16. A monomer is a building block of polymers. Monomers are linked together by chemical bonds to form polymers. Polymers are placed into two general categories: homopolymers and copolymers. Homopolymers are made up of a single monomer while copolymers are made up of two or more monomers. Copolymers are further divided into random copolymers, block copolymers and graft copolymers. A random copolymer is a polymer where the monomers are bonded together in a statistically random fashion.

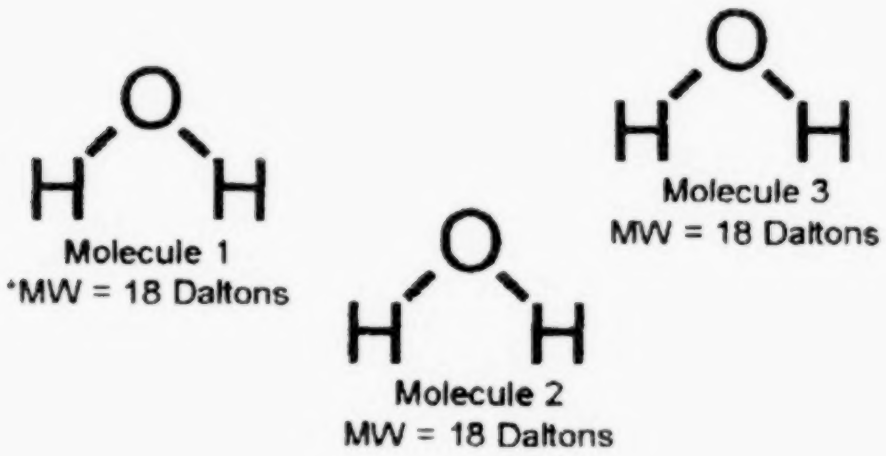
17. I understand that "copolymer-1" is the name given to a specific copolymer composition developed at the Weizmann Institute and reported in the

scientific literature in 1971. As described in the literature and in the Teva patents, copolymer-1 is a random copolymer composed of four amino acid monomers. The amino acids are L-alanine, L-lysine, L-glutamic acid, and L-tyrosine. The four amino acids are randomly bonded together to form molecules called "polypeptides." The polypeptides are "polydisperse" in that they exist as a macromolecular mixture of polymer chains that have varying molecular weights and chemical compositions. Hypothetically, if we can count the number of each individual amino acid in each macromolecular chain, one can calculate the molecular weight of each polymer chain. However, even if we can experimentally count the number of amino acids in each polymer chain, the molecular weight characterization of the "Copolymer-1" will be challenging because the "Copolymer-1" exists as mixtures of copolymer chains with a molecular weight distribution. Therefore, we have to rely on a chromatography analysis tool, such as GPC, to estimate the molecular weight distribution and calculate different types of average molecular weights.

A. Molecular Weight

18. The "molecular weight" of a molecule is defined as the sum of the atomic weights of the atoms that make up that molecule, expressed in the unit of "Daltons." Because of the polydispersity of copolymer-1, the individual polypeptide chains that compose copolymer-1 have different molecular weights. This is quite different than a monodisperse composition, such as water or biologically active enzymes/proteins, where the molecular weights of

each of the molecules are the same. For example, water contains identical molecules containing one oxygen (molecular weight of 16 Da) and two hydrogens (each molecular weight of 1 Da) for a total molecular weight of 18 Daltons per molecule of water:



* MW = molecular weight

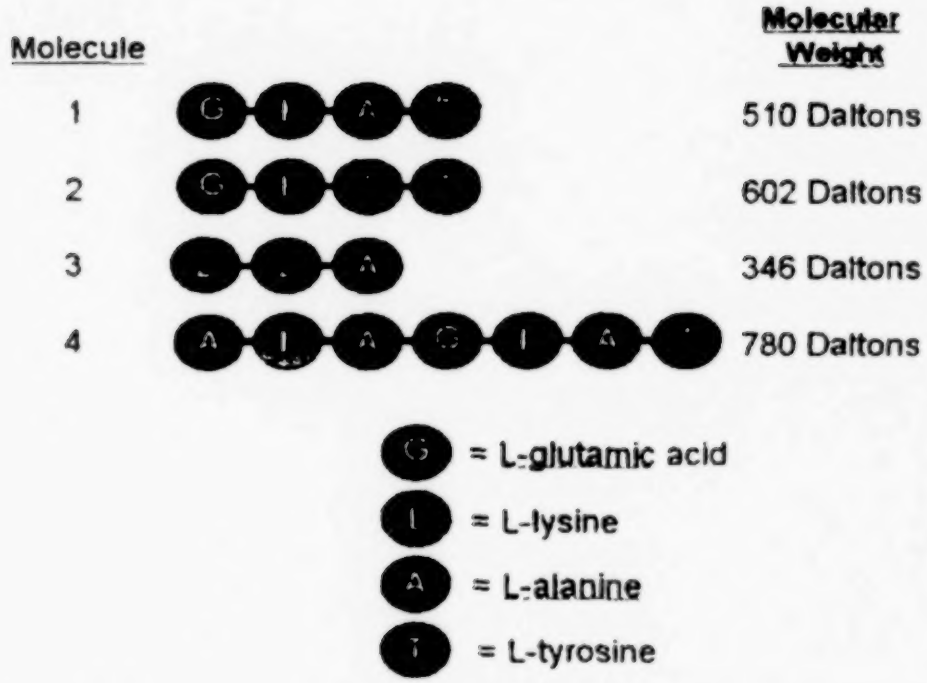
Each and every molecule in water thus has the same molecular weight of 18 g/mole or "18 Daltons."

19. In contrast, copolymer-1 is made up of polypeptides which have varying molecular weights. The molecular weight of a single polypeptide is insufficient to describe the molecular weight distribution of copolymer-1. For example, consider a simple illustrative example of copolymer-1 with four polypeptides (shown below). Molecules 1 and 2 contain 4 amino acids. Molecule 3 contains three amino acids. Molecule 4 contains 7 amino acids. The amino acid composition of each molecule is different. Therefore, even though molecules 1 and 2 have the same number of amino acids, each molecule has a different molecular weight. The molecular weights of

the polypeptides are calculated using the following table and formula, once the numbers of different types of amino acids in the peptide chain are known. Because water (MW = 18.0 Da) is lost after the formation of peptide bonds between adjacent amino acids, the molecular weight of each amino acid unit is used for the molecular weight calculation after water is being removed (i.e. the column of "MW less water" in the table). Finally, the molecular weight of water (i.e. 18.0 Da) has to be added for the calculation of the polypeptide molecular weights, because the peptide chain end still contains unreacted amine and carboxylic acid groups.

Amino acid	MW (Da)	MW less water (Da)	Symbol
L-Alanine	89.1	71.1	A
L-Lysine	146.2	128.2	L
L-glutamic acid	147.1	129.1	G
L-Tyrosine	181.1	163.1	T

Molecular weight (Da) = 71.1*(No. of A) + 128.2 * (No. of L) + 129.1 * (No. of G) + 163.1 * (No. of T) + 18.0



20. Like this example, since most polypeptides in copolymer-1 have a different molecular weight, the molecular weight of copolymer-1 is best described by either a molecular weight distribution or a combination of two or more different types of average molecular weights.

B. Average Molecular Weight

21. Initially, I note that it scientifically is incorrect to say that copolymer-1 has a single "molecular weight." Because it is a polydisperse mixture containing many different polypeptides, each of different molecular weights (as illustrated in my simple example above), it is incorrect to say that copolymer-1 has a single molecular weight. In 1994, if a person of ordinary skill read that copolymer-1 has a molecular weight, he or she would assume that the writer intended "average molecular weight." In addition, there are different kinds of "average

molecular weights" to represent the molecular weight distribution of polydisperse polymers and two or more kinds of "average molecular weights" typically are used to correctly describe the molecular weight distribution of polydisperse polymers, such as copolymer-1.

22. In 1994, experimentally determining the exact "average molecular weights" of polydisperse polymers such as copolymer-1 was in fact impossible. To do so, one would have to individually isolate and reliably detect each polypeptide making up copolymer-1, calculate its exact molecular weight, and then average each of the individual molecular weights together. There was no reliable technology, however, which could isolate even a single copolymer-1 polypeptide chain. Thus, unlike the examples above (with water and the four known polypeptides), a scientist in 1994 would not know what the amino acids are in each molecule and therefore could not calculate the molecular weight of any individual polypeptide or the true average molecular weight of the polydisperse mixture.

23. However, in 1994, there were several different ways to estimate the average molecular weights of a polydisperse polymer such as copolymer-1. The typical types of molecular weight averages which could be estimated included number average molecular weight (Mn), weight average molecular weight (Mw), z-average molecular weight (Mz), and viscosity average molecular weight (Mv).

24. Each type of average molecular weight for a given polymer could be estimated using certain experimental methods. For example, in 1994, Mn

was commonly estimated by measuring osmotic pressure or performing end group analysis. Mw was estimated using light scattering or sedimentation velocity experiments. Mz was estimated using sedimentation equilibrium and Mv was estimated by measuring the intrinsic viscosity.

25. By 1994, Gel Permeation Chromatography ("GPC") also had become a prevalent experimental tool to estimate the molecular weight distribution and the different average molecular weights of polymers. Gel permeation chromatography is also referred to as "gel filtration chromatography" ("GFC") and "size exclusion chromatography" ("SEC").

26. GPC is a "relative" measurement of the molecular weight of molecules in a polydisperse polymer such as copolymer-1. GPC is in fact not based on the weight of a molecule but rather on the hydrodynamic size of a macromolecular chain in dilute solution (i.e., the three-dimensional shape and size of the molecule). The molecular weight is estimated relative to a set of calibration standards. By comparing the rate at which molecules of unknown molecular weight migrate through a GPC column to the rate at which molecules of known molecular weight (referred to as "calibration standards" or "markers") migrate through the same column, scientists can estimate the molecular weight distribution of unknown polymers. Thus, a scientist would take a number of standards of different molecular weights and pass them through the GPC column. By measuring how long each standard would take to pass through the column (the "retention time"), the researcher could calibrate the

column. Following calibration, the researcher then could pass the unknown polymer through the column and by comparing the retention time of the unknown polymer to the retention time of the known calibration standards, an estimate of the molecular weight distribution and different average molecular weights of the polymer such as Mn and Mw could be obtained (discussed more below).

27. An important principle underlying GPC analysis is that the "shape" of the calibration standards should mimic the shape of the molecules in the unknown sample under the conditions used to run the GPC. Experimentally, however, in 1994 it was often difficult to meet this requirement because, in the first place, the polymer is unknown and hence the shape is unknown, and so one may not be able to determine the best calibration standards that have the same shape under GPC conditions. In addition, to enhance the fidelity of the GPC analysis results in characterizing unknown polymer samples, the GPC calibration standards (or GPC "markers") should have very narrow molecular weight distributions to be used in the GPC calibration plot to estimate the molecular weight distribution and average molecular weights of the polydisperse polymer samples to be analyzed. It is also important that the GPC calibration standards are composed of many well-characterized standards with a wide range of molecular weights to correctly estimate the molecular weight distribution in unknown polydisperse samples. The molecular weight ranges of the GPC calibration standards have to be wider than the molecular weight ranges of the unknown polydisperse samples to be analyzed.. Moreover, in

1994, there were only a limited number of commercially available calibration standards at different molecular weights and so there typically were a limited number of choices of what standard to use for a given molecular weight. Further, the standards used to calibrate the GPC column for one molecular weight could be a different kind of polymer than the standards for a different molecular weight and thus one standard might better approximate the shape of the polymer than another for one molecular weight. Also, under the different sets of experimental conditions that were typically used to run GPC, the shape of both the calibrations standards and unknown polymers could vary widely. Moreover, the variations of the calibration standards and unknown polymers between different experimental conditions used to run the GPC often were not the same, such that changing the experimental conditions in many cases could yield different average molecular weight values even though the standards and unknown polymer stayed the same. So, as discussed below, estimating the molecular weight distribution of polydisperse polymers by GPC can give widely varying results depending on the standards used and the conditions under which the GPC is performed.

28. When determining average molecular weight using GPC, the unknown polymer sample is dissolved in dilute solution and added by an GPC injector to one end of the column under pressure at a constant flow rate of elution solvent (e.g. 0.5 mL per minute). The polymer samples are being separated in the GPC column and the concentrations of each "fraction" in the GPC chromatography profile are

discretely measured by a concentration sensitive detector at a regular time interval until the detector signal returns back to a baseline to confirm the complete elution of the polymer samples from the GPC column. The detector time interval has to be very small and the sample of the GPC discrete data points are very frequent (e.g. typically more than 100 points per 1 mL of elution volume) in order for the researcher to assume that the each "fraction" in the GPC profile has a nearly monodisperse molecular weight. Using the calibration obtained from running the standards, an average molecular weight for each GPC fraction can be estimated and then plotted in a curve against the percent of the total mass of the unknown polymer obtained in that fraction. An example of such a curve is shown in Figure 1 of the Teva patents.

29. In addition to the above types of average molecular weight descriptors such as Mn and Mw, the term "Peak Molecular Weight" (Mp) is used to define the peak of the curve I described just above. To persons of ordinary skill in the field of determining average molecular weights of polydispersed polymers, Mp is less commonly used than Mn and Mw because the position of the peak is subject to uncertainty due to limited amounts of discrete data points in the vicinity of the peak. Hence, as I discuss more below, any Mp values obtained potentially can have significant error and uncertainty built into the value. In contrast, Mn and Mw have a well defined mathematical definition that allows a researcher to precisely calculate their numbers once the molecular weight distribution is fully known and reliable. Also, the ratio of Mw/Mn is

known as "polydispersity" or "polydispersity index" and is commonly used to describe the broadness of molecular weight distribution in polydisperse polymer samples, such as copolymer-1. In the example of Figure 1 of the Teva patents, the ratio of Mw/Mn would indicate how broad or narrow the peak of the molecular weight distribution curve will be. The closer the ratio is to 1, the narrower the peak. The greater the ratio, the broader the peak.

30. Further, in polydisperse mixtures that do not have a narrow molecular weight distribution, the curve in the area of the peak is not sharp and thus an accurate determination of the peak may not be feasible. There also can be practical limitations to model the position of the peak using existing mathematical models, especially if the curve is wide and asymmetrical. For all of these reasons, therefore, there can be an inherent inaccuracy in determining Mp.

31. For any given copolymer such as copolymer-1, the values of Mn, Mv, Mw, Mz and Mp typically will be different, sometimes by a considerable amount, e.g., where there is not a narrow molecular weight distribution.

C. Gel Permeation Chromatography Used to Determine the Average Molecular Weight and the Patents-in-Suit

32. I understand that descriptions or "specifications" of the patents in suit are essentially the same and so will refer in my declaration only to the specification of U.S. Patent No. 5,800,808 to ("the '808 patent") unless otherwise noted. I note that the '808 patent issued on September 1, 1998.

1. **The reference to an average molecular weight of 23,000 daltons for copolymer-1**

33. The '808 patent does not describe which "average molecular weight" of copolymer-1 is being referred to in the instances where it refers to average molecular weight. Additionally, the '808 patent references average molecular weights in two contexts. First, when discussing US Patent No. 3,849,550 (the '550 patent). Second, when discussing the copolymer-1 compositions analyzed in the Teva patents.

34. At column 1, lines 32-37, the '808 patent states:

> Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

35. U.S. Patent No. 3,849,550 ('the '550 patent) also does not state which average molecular weight is being reported, but does report at column 2, lines 19-22 an average molecular weight of about 20,000 to about 25,000, which is consistent with the above statement in the '808 patent:

> A preferred copolymer according to the present invention comprises in combination alanine, glutamic acid, lysine and tryosine, of net overall positive electrical charge with an amino acid without electrical charge and of a molecular weight of about 20,000 to 25,000.

36. I note that the above passage of the '550 patent uses the term "molecular weight" instead of "average molecular weight" but for the reasons I discuss above, it is clear that the reference to "molecular weight" is actually to "average molecular weight."

37. I note that the '550 patent references the 1971 publication by Dvora Teitelbaum et al., Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide, Eur. J. Immunol. 1971. 1: 242-248 ("Teitelbaum 1971"). I have reviewed Teitelbaum 1971 which also reports an average molecular weight for copolymer-1 of 23,000. This is consistent with the average molecular weight values reported in the '808 and '550 patents as discussed above. I further note that Drs. Teitelbaum, Arnon and Sela are all named inventors on the '808 patent, the '550 patent and named authors of Teitelbaum et al. 1971. Also, the '808 patent twice references Teitelbaum et al. 1971 as containing the procedure for making protected copolymer-1. See column 4, lines 30-35 and 49-53, which both state:

> Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), y-benzyl glutamate (35 g) and tritluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

38. Teitelbaum et al. 1971 states that the average molecular weight of 23,000 was determined by ultracentrifugation (see page 244):

3.7. Molecular weight determinants

The average molecular weights of the polymers were determined, in a Spinco model E ultracentrifuge, from sedimentation and diffusion measurements, as described earlier [24], and by the approach to equilibrium technique of Yphantis [29].

39. From this description in Teitelbaum et al. 1971, I conclude that the average molecular weight of 23,000 referred to in the '808 patent, as well as the average molecular weights described in the '550 patent, are referring to average molecular weight as determined by ultracentrifugation. Ultracentrifugation can provide weight average molecular weight or z-average molecular weight, but cannot provide peak molecular weight.

2. **The reference to average molecular weight determined by gel filtration column**

40. The '808 patent also discusses the average molecular weight of copolymer-1 compositions by use of gel filtration column in column 3, lines 3-18 (underlining added):

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of

this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

41. The '808 patent does not state which average molecular weight was determined by gel filtration chromatography. As noted above, GFC can determine multiple types of average molecular weights including weight average molecular weight and number average molecular weight, as well as peak molecular weight, which as described above, is not an average molecular weight but rather a point taken from a plot of the molecular weight distribution curve.

3. There is nothing in the '808 patent to indicate which average molecular weight is being referred to

42. I understand that Teva has asserted that the average molecular weight would be understood to be a peak molecular weight. Figure 1, however, which is the only plot from which Mp might be derived, does not show peaks of either 7.7 kDa or 12.0 kDa, which are the reported average molecular weights. There is nothing in the Teva patent specification which can explain the discrepancy in Teva's argument.

4. **The prosecution histories do not clarify the ambiguity**

43. I have reviewed the prosecution histories of the nine patents in suit, and especially on certain passages. Overall, the prosecution histories do not clarify which average molecular weight is being referred to with respect to GFC.

44. During the prosecution of the seventh Teva patent to issue, i.e., U.S. Patent No. 6,620,847 ("the '847 patent"), Teva stated in a response filed June 26, 2002 that the phrase "a molecular weight of about 4 to about 9 kilodaltons" is a weight average molecular weight: "One of ordinary skill in the art could understand that kilodalton units implies a weight average molecular weight."

45. I understand that Teva has asserted that the reason that they gave the Patent Office is incorrect because the kilodalton units do not necessarily imply a weight average molecular weight. Although kilodalton units do not necessarily imply a weight average molecular weight, weight average molecular weight is reported in kilodaltons and can be determined by the gel filtration chromatography mentioned in the specification. Nevertheless, the person of ordinary skill would still consider weight average molecular weight as one possible average molecular weight referred to in the patents. This is especially true since the curves in Figure 1 of the patents show the peak molecular weights to be lower than 7.7 kilodaltons and 12 kilodaltons and since weight average molecular weight is known to be greater than peak molecular weight.

46. During the prosecution of the eighth Teva patent to issue, i.e., U.S. Patent No.6,939,539 ("the '539 patent"), Teva stated in an response filed December 1, 2004 that the phrase "average molecular weight" is a peak molecular weight: "One of ordinary skill in the art, upon reviewing the specification, would understand that "average molecular weight" refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1, which is "% of total mass" versus "molecular weight" As shown in Figure 1, the "average molecular weight" is 7.7 kDa for the separated copolymer-1 ("Batch A") described in Example 1, and 12.0 kDa for the unseparated copolymer-1."

47. However, I note that the assertion that the molecular weight is Mp also would appear to a person of ordinary skill to be an incorrect statement, as the peaks in the curve in Figure 1 are not at either 7.7 or 12 kDa.

48. In sum, for the reasons discussed above, I do not see that the prosecution histories would inform a person of ordinary skill in the art which average molecular weight is being used in the specification and patent claims (except that the reference to copolymer-1 having an average molecular weight of 23,000 daltons, which as I described above, is clearly a reference to average molecular weight determined by ultracentrifugation).

D. <u>The description of determining average molecular weight by gel filtration column is insufficient for a person of ordinary skill to make a valid and reproducible determination of average molecular weight</u>

49. As mentioned above, example 1 of the '808 patent is the only disclosure in the specification of how the average molecular weight of the copolymer-1 batches in this patent are estimated. This is provided at column 3, lines 3-8 (underlining added):

> Molecular Weight Analysis
>
> UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. <u>The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12)</u>.

50. I further note that the '808 patent discloses no other necessary experimental details that would be required for the person of ordinary skill to reproduce this GFC analysis. Such necessary details include both the specific GFC operating conditions and the identity of the calibration standards used.

51. As noted above, because GFC is a relative measurement, the molecular weight estimates are dependent entirely on the calibration of the GFC column. GFC operating conditions, including the chemical properties of the buffer such as the pH, salt concentration, and temperature, and the physical parameters of the instrumentation such as the flow rate, sample concentration, column dimensions, and

injection volume can have dramatic effects on GFC analysis. Likewise, knowing the identity of the calibration standards including their polydispersity and average molecular weights to warrant their narrow molecular weight distribution is critical for reproducibility.

52. As stated above, GFC does not directly measure molecular weights of polymer molecules rather it separates the polymer molecules based on the differences in their hydrodynamic volume in dilute solution. Small differences in the hydrodynamic size of the polymer molecules can substantially affect the estimation of molecular weights in the GFC profile and thus influence the correct estimation of average molecular weights from GFC experiment.

53. To my knowledge, calibration standards that mimicked the shape of copolymer-1 molecules were not commercially available in 1994.

54. It also is not clear from either the '808 patent or the knowledge in the art in 1994 what combination of GFC operating conditions and calibration standards one would use to reproduce the analysis in the '808 patent. In 1994, there would have been literally hundreds of combinations available to perform the GFC experiment, many of which would have yielded different average molecular weight values. And because the molecular weight distribution curve would have changed in many instances, the peak molecular weight would have varied in many instances.

E. Use of a Test Reaction to make low molecular weight copolymer-1 indicates protected copolymer-1 compositions vary from batch to batch

55. The '808 patent states at column 4, lines 31-39 and again at 49-58:

> Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), y-benzyl glutamate (35 g) and tritluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.
>
> The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried."

56. The '808 patent then states at column 4, line 59 to column 5, line 8 (underlining added):

> Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000.+-.2,000 Da depends on the reaction temperature and the size of protected copolymer-1. <u>At temperatures of between 20-28.degree. C. a test reaction is performed on every batch at different time periods for example, from 10-50 hours.</u>

> The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000.+-.2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26.degree. C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

57. One of ordinary skill in 1994 reading the above passages would clearly understand that the composition of protected copolymer-1 varies from batch to batch. First, one of ordinary skill understands that a polymerization reaction such as that described in Teitelbaum 1971 simply will yield protected copolymer-1 that varies from batch to batch.

58. Second, the inventors clearly recognized that because they described performing a test reaction. "on every batch" of protected copolymer-1. One of ordinary skill would expect that a reaction would not have to be run on every batch if there were no variation from batch to batch.

59. A person of ordinary skill also would understand that the inventors intended to run a test reaction on every batch of protected copolymer-1 to determine what amount of time and what temperature would yield the desired profile for that batch so that they then could apply that information to the rest of that batch. A person of ordinary skill would not expect that the information from the test

reaction from one batch would be used on another because of the variation from batch to batch.

Dated this 20th day of April, 2010.

_____

Chang Ryu, PhD.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs,* v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., *Defendants.*	Civil Action No. 09-CV-8824 (BSJ) (AJP) **Filed Under Seal (External Counsel Only)**

SUPPLEMENTAL DECLARATION OF GREGORY A. GRANT, PH.D.

1. I, Gregory A. Grant, submit this supplemental declaration to provide my opinion on behalf of Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., (collectively, "Teva") and Yeda Research and Development Co. (collectively, "Plaintiffs").

2. I have previously provided a declaration, executed and dated April 19, 2010 ("first Declaration") in connection with the patents-in-suit,

and expressly incorporate that declaration in its entirety.

3. My opinions are based on my review of the declarations of Dr. Chang Ryu and Dr. Jerard Hurwitz submitted by the Defendants ("the Ryu Declaration" and "the Hurwitz Declaration," respectively), as well as my knowledge, education, and experience, the references listed in Exhibit 1, and the materials previously identified in my first Declaration.

I. ONE OF ORDINARY SKILL IN THE ART WOULD HAVE UNDERSTOOD AVERAGE MOLECULAR WEIGHT TO MEAN PEAK AVERAGE MOLECULAR WEIGHT IN THE CONTEXT OF THE PATENTS-IN-SUITS

4. Dr. Ryu states in his declaration that "the molecular weight of copolymer-1 is best described by either a molecular weight distribution or a combination of two or more different types of average molecular weights." (Ryu Decl., ¶ 20.) I do not know precisely what Dr. Ryu means by "best described,' but in my opinion, one could also describe the molecular weight of copolymer-1 by a molecular weight distribution, including identification of the peak average molecular weight.

5. In their brief, Defendants point to a reference in the '808 patent specification to the prior art copolymer-1 described in Teitelbaum 1971, which determined an average molecular weight through ultracentrifugation. (Defs.' Br. at 11.) They suggest that because ultracentrifugation can be used to determine weight average or z-average molecular weight but not peak molecular weight, the claims of

the patent could refer to something other than peak molecular weight. I disagree with this suggestion. The specification is clear when discussing the patented inventions that molecular weight is to be measured by SEC, not ultracentrifugation. ('808 patent, col. 3, lines 6-8.)

6. In their brief, Defendants characterize my earlier deposition testimony as a "concession" that average molecular weight can refer to several different types of average molecular weight. (Defs.' Br. at 12.) The question I was asked at that deposition was not limited to SEC or any other measurement method. In the absence of an identification of the method, it is true that "average" could refer to more than one type of average. But in the context of the patents-in-suit, it is my opinion that peak average molecular weight would be understood to be the meaning of "average molecular weight" if the type of average is not specified.

7. Dr. Ryu states that a person of ordinary skill would consider weight average molecular weight as one possible average molecular weight referred to in the patents "since the curves in Figure 1 of the patents show the peak molecular weights to be lower than 7.7 kilodaltons and 12 kilodaltons and since weight average molecular weight is known to be greater than peak molecular weight." (Ryu Decl., ¶45.) I disagree. One of ordinary skill in the art would have understood that peak average molecular weight refers to the molecular weight at the apex of a chromatogram. Although the peak average molecular weight (Mp) conceptually corresponds to the apex of a molecular weight distribution curve, the transformation from a chromatogram to a

distribution curve such as those depicted in Figure 1 could have resulted in a shift in the peak. (*See* my first Declaration (D.I. 39), ¶¶ 43-53). Thus, the fact that the number in the legend and the peak of the curve are not the same is not unexpected.

II. A PERSON OF SKILL IN THE ART OF THE PATENTS-IN-SUIT WOULD HAVE BEEN ABLE TO CHOOSE APPROPRIATE STANDARDS AND CONDITIONS FOR SEC MEASUREMENT OF COPOLYMER-1

8. Defendants' experts assert that the patent specification does not set forth standards and conditions for carrying out SEC to determine molecular weight, and in particular, does not set forth the precise standards and conditions used by the inventors so that they can be replicated by a person of skill in the art. (*See, e.g.*, Ryu Decl. ¶¶49-54; Hurwitz Decl. ¶¶ 14-24.) It is my opinion that a person of skill in the art in 1994 would have known how to select appropriate standards and use appropriate conditions for size exclusion chromatography ("SEC") in order to measure the molecular weight of a sample of copolymer-1 and determine whether it met the molecular weight elements of the claims. It is further my understanding that there is no requirement that a patent set forth the precise standards and conditions used by the inventors as long as one of ordinary skill in the art is able to practice the patented invention.

9. As I have previously stated, and as Defendants' experts recognize, the level of skill in the art of the patents-in-suit is high. (*See, e.g.*, my first Declaration (D.I. 39), ¶ 21; Ryu Decl., ¶ 14; Hurwitz

Decl., ¶ 8.) A person of skill would have understood the SEC technique thoroughly and would not have required a detailed explanation of how to use SEC to determine whether a sample of copolymer-1 had the claimed molecular weight characteristics. Persons of skill in the art would have understood how to select appropriate standards and conditions and how to appropriately carry out an SEC analysis to determine the molecular weight of an unknown.

10. The patents-in-suit claim copolymer-1 having certain molecular weight characteristics and methods of making and using copolymer-1 having certain molecular weight characteristics. The patents describe the use of a well-known method for determining the molecular weight characteristics of copolymer-1: size exclusion chromatography. The patents state that molecular weight distribution of copolymer-1 "was determined on a calibrated gel filtration column (Superose 12)." ('808 patent, col. 3:6-7.)

11. In 1994, SEC was commonly accepted as an appropriate technique for assessing the molecular weight characteristics of a polymer sample. It was and still is, in my opinion, the most appropriate technique for measuring the molecular weight distribution of polydisperse analytes, such as copolymer-1. Conducted in an appropriate manner, which would have been well-understood in 1994, SEC provides results that accurately reflect the molecular weights of such mixtures.

12. A person of skill in the art would have understood from the disclosure of the patents-in-suit that he should use an appropriately calibrated

suitable gel filtration column to determine whether a given sample of copolymer-1 has the molecular weight characteristics identified in the claims. The person of skill would have understood the molecular weight values listed in the patent claims to refer to accurate molecular weights, as opposed to apparent molecular weights.[18] The person of skill would have understood that they could use more than one set of standards and/or conditions to obtain accurate results, *i.e.*, that their analysis was not limited to the use of a single set of standards and conditions, and such results, although obtained relative to the calibration standards, reflect the true molecular weight characteristics of the sample. The person of skill in the art would have known that he could use either self-standards or universal calibration, and that any of a number of appropriate conditions could be used.

A. A Person of Skill Would Have Known How To Select Appropriate Standards

13. I have reviewed paragraphs 14-24 of the Hurwitz Declaration and paragraphs 49¬54 of the Ryu Declaration. I disagree with their conclusions that disclosure of the standards and conditions used to perform the SEC analysis described in the patents is necessary. I also disagree with the suggestion that the exact standards and conditions used for the SEC

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[18] By "accurate", I mean a molecular weight obtained by SEC that reflects the true molecular weight characteristics of the sample. By "apparent", I mean a molecular weight obtained by SEC that reflects a value relative to a standard that is not necessarily an appropriate standard, *i.e.*, one that does not share the hydrodynamic characteristics of the sample being measured.

analysis described in the patents would need to be reproduced in order to determine the scope of the patent claims.

14. SEC was well described in the literature in 1994. It was well known prior to 1994 that in order to generate data accurately reflecting the underlying molecular weight of the components of a sample, SEC standards should be chosen that have a similar relationship between molecular weight and hydrodynamic volume as that of the sample to be measured. (*See, e.g.*, Jansen & Ryden, Protein Purification, Ch. 3, Gel Filtration (1989) (attached as Ex. 2); Yau *et al.*, Modern Size-Exclusion Liquid Chromatography, Ch. 9 (1979) (attached as Ex. 3).) I note that Defendants' experts agree. (*See* Hurwitz Decl., ¶ 16; Ryu Decl., ¶ 27.) There is not one unique set of standards that must be used to accurately measure the molecular weight of any particular sample. Rather, the person of skill would have known that one must choose standards that approximate the hydrodynamic volume-to-molecular weight relationship of the substance being measured, or otherwise account for the differences in that relationship, in order to make an accurate determination of the molecular weight of the sample. (*See, e.g.*, Yau, Ex. 3) A person of ordinary skill in the art in 1994 attempting to determine whether a particular sample of copolymer-1 met the molecular weight characteristics set forth in the claims of the patents-in-suit would have known that they could use either self-standards or existing commercial standards in conjunction with universal calibration in order to obtain an accurate molecular weight. The use of both self-standards and universal calibration

was well known to persons of ordinary skill in the art in 1994. (*See, e.g.*, Billingham, Molar Mass Measurement in Polymer Science, Ch. 8 (1977) (attached as Ex. 4); Rubio, *et al*, Size Exclusion Chromatography of Copolymers, Advances in Chemistry Series, 201:311-344 (1983) (attached as Ex. 5); Chiantore and Hamielec, Molecular Weight Calibration of SEC Using Broad MWD Standards - Application for Poly (P-Methyl Styrene), *Journal of Liquid Chromatography*, 7:1753-1757 (1984) (attached as Ex. 6); Provder, Chromatography of Polymers, Ch. 8 (1993) (attached as Ex. 7).)

15. In 1994, the person of skill would have understood that the use of self-standards would have provided accurate molecular weight results. As the name implies, self-standards are standards of the same substance as the sample to be measured, and they could include fractions of the substance to be analyzed or separate samples of the substance. Self-standards can include fractionated polymer with relatively narrow molecular weight distributions or unfractionated polymer with relatively broad molecular weight distributions. (*See* Billingham, Ex. 4.) A person of skill in the art would have understood how to fractionate copolymer-1. The patents-in-suit teach how to make copolymer-1 having certain molecular weight characteristics and how to control the molecular weight of copolymer-1. The molecular weights of the self-standards are measured using an absolute measurement technique. One example of such a technique is mass spectrometry, but other techniques such as light scattering were available to persons of skill in the art in 1994. (*See, e.g.*, Barth and Mays, Modern Methods of Polymer

Characterization, Ch. 9 (1991) (attached as Ex. 8); Hillenkamp and Karas, Mass Spectrometry of Peptides and Proteins by Matrix-Assisted Ultraviolet Laser Desorption/Ionization, *Method in Enzymology*,193:280 (1990) (attached as Ex. 9); Gelpi, From large analogical instruments to small digital black boxes: 40 years of progress in mass spectrometry and its role in proteomics. Part II 1985-2000, 44: 1137) (2009) (attached as Ex. 10); Burger, *et al.*, Matrix-Assisted Laser Desorption and Ionization as a Mass Sectrometric Tool for the Analysis of Poly[(i?)-3-hydroxybutanoates]. Comparison with Gel Permeation Chromatography, *Macromolecules*, 26: 4783-90 (1993) (attached as Ex. 11).)

16. Dr. Ryu states in his declaration that "the molecular weight ranges of the GPC calibration standards have to be wider than the molecular weight ranges of the unknown polydisperse sample to be analyzed." (Ryu Decl., ¶ 27.) I disagree. To obtain the peak molecular weight of a sample using SEC, it is not necessary for the molecular weights of the standards to encompass the entirety of the molecular weight range of the unknown sample.

17. Dr. Hurwitz states in paragraph 22 of his declaration that "the identity of the calibration standards that is used must be known to be able to compare data obtained in SEC different [sic] experiments." I disagree. The claims are not limited to copolymer-1 having particular molecular weight characteristics as measured by Teva or as measured using standards and conditions identical to those used by Teva at some point in time. A person of ordinary skill in the art in 1994 would have known

how to choose appropriate standards to measure the molecular weight characteristics of copolymer-1. Therefore, it does not appear to me to be necessary for the public to know what standards Teva used.

18. In their brief, Defendants point to Teva's later-filed patents ("the Gad patents") claiming peptide calibration standards ("TV-markers") as evidence that different standards yield different molecular weight values for copolymer-1. (Defs.' Br. at 15-16.) In my experience, there is inherent variation in molecular weight determinations made using SEC, even when the same standards and conditions are used. It is my opinion that the variation between the molecular weight values obtained using the TV-markers and the glatiramer acetate molecular weight markers (as referenced in the Gad patents) is within the inherent variability in SEC measurement of molecular weight values that would be expected even when the same set of markers is used.

19. In 1994, a person of skill in the art could also have used commercially-available standards and universal calibration to assess the molecular weight characteristics of a sample using SEC. Universal calibration is a technique that allows comparison of hydrodynamically dissimilar substances by employing conversion factors based on the intrinsic viscosities of the sample and the standards. (*See, e.g.*, Billingham, Ex. 4.) Measurement of intrinsic viscosity would have been a routine matter for a person of ordinary skill in the art in 1994. (*See, e.g.*, Barth and Mays, Modern Methods of Polymer Characterization, Ch. 1 (1991) (attached as Ex. 12).)

B. A Person of Skill Would Have Known How to Select Appropriate Conditions

20. In paragraph 23 of his declaration, Dr. Hurwitz states that "the reproducibility and validity of the molecular weight measurements so obtained are compromised" if the conditions used for determining molecular weight on an SEC column are not clearly defined. (*See also*, Ryu Decl., ¶¶ 51, 54.) He does not clarify what this means precisely. To the extent that he is offering the opinion that a person of skill would have to have all of the conditions for a molecular weight analysis detailed for them, I disagree. In my opinion, a person of ordinary skill in the art of the patents in suit (which is a high level of skill) would have known how to select and apply appropriate conditions for determining molecular weight using SEC without such conditions (or the calibration standards) being set forth in detail. The person of skill would have known how to select and adjust conditions such as column packing, column dimensions, sample volume, flow rate, pH and salt concentration. In addition, the person of skill would have known that samples and standards should be treated under the same conditions. (*See* Yau *et al.*, Ch. 9 at 288, Ex. 3.) I note that Defendants' experts agree. (Ryu Decl., ¶ 26; Hurwitz Decl., ¶ 16.)

21. In addition, in the event that the conditions used caused the polypeptides to be separated on the basis of something other than size, a person of skill in the art would have known how to recognize this result and adjust conditions accordingly. For example, if separation was based on electrostatic interactions, a person of skill could have recognized this by noting that the sample elutes much later

than expected, such as eluting after the inclusion volume of the column. A person of skill would have known how to adjust SEC conditions to correct for such electrostatic interactions by, for example, increasing the ionic strength or changing the gel matrix. As another example, one would know *not* to overload the column and to adjust the concentration of the analyte so that valid results are obtained.

22. A person of skill in the art would have been able to recognize whether results were valid by analyzing the data for both the sample and the standards and by determining the results of varying conditions, which would have been standard practice. For example, Pharmacia, Gel Filtration: Principles and Methods (1993) (attached as Ex. 13), includes a Troubleshooting section showing the differences between a chromatogram showing satisfactory separation and chromatograms that are indicative of problems such as inappropriate column volume, flow rate, overpacking, uneven sample application and binding to the gel filtration medium. There are ample examples in the literature where similar troubleshooting approaches are discussed. (*See, e.g.*, Yau *et al.*, Modern Size-Exclusion Liquid Chromatography, Ch. 8 (1979) (attached as Ex. 14); Stellwagen, Gel Filtration, *Methods in Enzymology*, 182: 317-328 (1990) (attached as Ex. 15).) A person of skill in the art in 1994 would have been familiar with these potential problems and could have recognized their presence, for example, by visual inspection of a chromatogram. It would have been routine for a person of skill to adjust SEC conditions in order to address these issues.

23. There is not one unique set of SEC conditions that must be used to accurately measure the molecular weight of any particular sample. To illustrate how persons of skill in the art could employ varying SEC standards and conditions to measure the molecular weight of a particular sample and reach consistently accurate results, I performed a brief review of the literature on two widely-studied proteins: glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and L-lactate dehydrogenase (LDH). The results of this brief review were as follows:

a. A review of six articles published between 1964 and 2009 discussing SEC measurements of GAPDH shows that different scientists used different columns (where stated)[19], different calibration standards (where stated) and different SEC conditions (where stated) to measure the molecular weight of GAPDH, and their results ranged from 137 kDa to 148 kDa. I calculated the actual molecular weight of GAPDH (by summing up the molecular weights of the amino acid residues making up the protein) to be 143-144 kDa. The variation in the actual molecular weight is due to amino acid differences in this protein depending on the species from which it was derived. The articles are attached as Exhibits 16a-16f hereto.

b. A review of four articles published between 1972 and 2001 discussing SEC measurements of LDH shows that different scientists used different columns, different calibration standards (where stated) and different SEC conditions (where stated)

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[19] The SEC standards and conditions were not always stated in the articles.

to measure LDH, and their results for the monomer subunit ranged from 33 kDa to 35.5 kDa. The actual molecular weight was calculated to be 34-36.5 kDa. The articles are attached as Exhibits 17a-17d hereto.

24. These articles demonstrate two points: first, that persons of skill in the art would not have found it necessary to state the standards and/or conditions used when reporting molecular weight measurements for SEC analyses[20], and second, that there is no unique set of SEC standards and conditions that must be used in order to obtain accurate and consistent molecular weight results for a given polymer. Thus, I disagree with paragraph 23 of Dr. Hurwitz's Declaration, in which he states that "a person of ordinary skill in the art must be provided with specific details of the calibration standards, buffer composition, temperature, flow rate and the like to be able to make a reliable comparison with molecular weight data obtained using SEC methods." Meaningful comparisons of data between laboratories can be made without knowledge of the standards and conditions used.

25. Dr. Hurwitz states that "the standards and conditions used to perform the fractionation step must be defined" in order for the results to be "valid

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[20] I note that Dr. Ryu himself has published articles reporting SEC measurements in which he did not disclose the standards and conditions that he used. See, *e.g.*, Kim *et al.*, Chemical Composition Effects on the Fracture of Polystyrene-block-poly(methyl methacrylate) Block Copolymers, J. Polym. Sci.:Polym. Phys. Ed., 44(24):3612-3620 (2006) (attached as Ex. 19); Viswanathan *et al.*, Single-step In Situ Synthesis of Polymer-grafted Single-wall Nanotube Composites, J. Am. Chem. Soc., 125(31):9258-9259 (2003) (attached as Ex. 20).

and reproducible." (Hurwitz Decl., ¶ 17; see also Ryu Decl., ¶ 50.) Insofar as he is referring to valid results for the measurement of the molecular weight of a sample (as opposed to an attempted reproduction of someone else's calibration curves), I disagree that any particular set of conditions must be specified for a given sample in order to obtain valid molecular weight results using SEC. A person of ordinary skill in the art in 1994 would have known that any appropriate set of conditions could be used, and that the same conditions should be applied to both the sample and the calibration standards (also called calibrants), as acknowledged by Dr. Hurwitz (¶ 16). (*See* Yau *et al.*, Ch. 9 at 288, Ex. 3.)

26. Dr. Ryu (in paragraph 27 of his report) states that the sample and the standards can be impacted differently by SEC conditions. Without citation, Dr. Ryu states that "under the different sets of experimental conditions that were typically used to run GPC[21], the shape of both the calibrations [sic] standards and unknown polymers could vary widely." This would be very unlikely to occur with self-calibration, where the sample and the standards are the same. Where the sample and the standards differ, as in universal calibration, a person of skill would know to choose conditions that do not have such theoretically disparate impacts. Moreover, this is not a significant concern. It is a premise of SEC that the sample and appropriately selected standards will be affected similarly if they are run

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[21] Dr. Ryu refers to SEC as "GPC", or gel permeation chromatography.

under the same conditions. This allows scientists to rely on SEC results, as they have done for decades.

III. THE PEAK, NUMBER, AND WEIGHT AVERAGE MOLECULAR WEIGHTS OF MYLAN'S PROPOSED GENERIC PRODUCT ALL FALL WITHIN THE CLAIMED RANGES

27. I have reviewed excerpts of Defendants' ANDA, including Section 2.1, entitled "Molecular Weight Determination." (attached as Ex. 18.) Table 4 of ANDA Section 2.1 lists, among other data, the Mn , Mw, and Mp results for Mylan's glatiramer acetate Lot #s GMA/001/09, GMA/002/09, and GMA/003/09. (Ex. 18 at MYL0000113.) The peak molecular weights, number average molecular weights, and weight average molecular weights of these lots all fall within the range of "about 4 to about 9 kilodaltons," the range of "about 5 to about 9 kilodaltons," and the range of "about 5 to 9 kilodaltons."

IV. A TEST REACTION NEED NOT BE PERFORMED ON EVERY BATCH

28. The '808 patent states at col. 4, line 59 col. 5, line 5:

> Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20°-28° C. a test

> reaction is performed on every batch at different time periods for example, from 10-50 hours.
>
> The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction.

I understand this passage to say that by varying the time and temperature of the reaction of protected copolymer-1 of a given size (molecular weight) with HBr in acetic acid, one can obtain copolymer-1 of a desired molecular weight. The inventors reacted protected copolymer-1 with HBr in acetic acid for various time and at temperatures and measured the resulting molecular weights of copolymer-1. They then plotted this information and used it to perform larger scale reactions. In my opinion, once a test reaction has been performed on protected copolymer-1 of a given molecular weight at a particular temperature for a certain time, that information may be applied to any number of other (larger) batches of protected copolymer-1 having similar molecular weight. Thus, it is not necessary to perform a test reaction on every batch, as long as the conditions (time, temperature and protected copolymer-1 size) remain essentially constant.

29. Dr. Ryu states that one of ordinary skill in 1994 reading the passage cited in paragraph 23 above "would clearly understand that the composition of protected copolymer-1 varies from batch to batch." (Ryu Decl., ¶ 57.) It is not clear to me what Dr. Ryu is referring to by "composition of

protected copolymer-1." It is my understanding that the molar ratio of the amino acids comprising protected copolymer-1 would remain constant, and if each batch is made under the same conditions, the molecular weight characteristics of protected copolymer-1 should not vary significantly from one batch to the next.

I declare under penalty of perjury that the factual statements contained herein are known by me or believed by me to be correct.

DATED: May 20, 2010 _____

Dr. Gregory A. Grant

[EXHIBITS 16-17 OMITTED]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs/Counterclaim-Defendants,* v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., *Defendants-Counterclaim-Plaintiffs.*	Civil Action No. 09-CV-8824 (BSJ) (AJP) **FILED UNDER SEAL**

SECOND DECLARATION OF CHANG RYU, PH.D.

1. I have been retained by Perkins Coie LLP to provide my opinions as an expert witness on behalf of Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (collectively, "Defendants") regarding certain issues that pertain to U.S. Patents Nos. 5,800,808 ("the '808 patent"), 5,981,589 ("the '589 patent"), 6,048,898 ("the '898 patent"), 6,054,430

("the '430 patent"), 6,342,476 ("the '476 patent"), 6,362,161 ("the '161 patent"), 6,620,847 ("the '847 patent"), 6,939,539 ("the '539 patent"), and 7,199,098 ("the '098 patent"). I will refer to these patents collectively as "the '808 patent" unless indicated otherwise. I previously submitted an expert witness declaration dated April 20, 2010 ("First Expert Declaration"). I now submit the following additional expert witness declaration on behalf of Defendants.

I. EDUCATION AND EXPERIENCE

2. My qualifications are described in my First Expert Declaration, which I incorporate herein by reference. I am currently an Associate Professor in the Department of Chemistry and Chemical Biology at the Rennsselaer Polytechnic Institute ("RPI") in Troy, New York. I am also a faculty member of New York State Center for Polymer Synthesis and National Science Foundation Nanoscale Science and Engineering Center. For the last twenty years, my research has utilized gel permeation chromatography (GPC) for the analysis of synthetic homopolymers and copolymers that have polydisperse molecular weight distributions. A copy of my curriculum vitae, which lists my publications and describes my qualifications in detail, is attached as Exhibit 1 to my First Expert Declaration.

II. ASSIGNMENT

3. I have been tasked by Defendants to analyze, review and consider the opinions stated in Declaration of Gregory A. Grant, Ph.D. dated April

19, 2010 ("Grant Declaration") (Exhibit 1), which was submitted on behalf of Teva Pharmaceutical USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. and Yeda Research and Development Co. Ltd. (collectively, "Plaintiffs").

4. I have reviewed the Grant Declaration and considered the opinions stated within that declaration. In response to the Grant Declaration, I now provide the following additional opinions. In formulating my opinions, I have also considered the '808 patent (Exhibit 2 in my First Expert Declaration) and prosecution histories of the patents in suit. A detailed list of the materials I have reviewed in preparation of this second report is attached as Exhibit 2.

III. STATEMENT OF OPINIONS AND BASES IN SUPPORT

A. Claim phrases referring to the molecules making up copolymer-1 ("molecular weight")

- **"over 75% of its molar fraction within the *molecular weight* range from about 2kDa to about 20 kDa"**
- **"less than 5% of *species of copolymer-1 having a molecular weight* of over 40 kilodaltons"**
- **"wherein less than [2.5%] [5%] of the polypeptides of the mixture, on a molar**

fraction basis, have a *molecular weight* of over 40 kilodaltons"[22]

5. Dr. Grant states that a person of ordinary skill in the art would understand the term "molecular weight" to be the "the sum of the atomic weights of the atoms making up a molecule" (Grant Declaration ¶ 63). As discussed below, this definition does not apply when describing a polydisperse synthetic polymer, such as copolymer-1 (COP-1).

6. A person of ordinary skill in 1994 would distinguish between two meanings of the term "molecular weight" – a ***true*** molecular weight for a small-sized compound and an ***apparent*** molecular weight for a polymer. The different meaning for molecular weight for a polymer compared to that of a small-sized compound has been clearly articulated by George Odian in his book titled "Principles of Polymerization (1981)," which is one of the widely known polymer chemistry books.

> When one speaks of the molecular weight of a polymer, one means something quite different from that which applied to small-sized compounds. Polymers differ from the small-sized compounds in that they are polydisperse or heterogeneous in molecular weight. Even if a polymer is synthesized free from contaminants and impurities, it is still not a pure substance in the usually accepted sense. Polymers, in their

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[22] These three example claim phrases refer to claim terms 18, 21, and 9 listed in the Joint Claim Construction Chart submitted on April 2, 2010.

> purest form, are mixtures of molecules of different molecular weight. The reason for the polydispersity of polymers lies in the statistical variations present in the polymerization process. When one discusses the molecular weight of a polymer, one is actually involved with its average molecular weight. Both the average molecular weight and the exact distribution of different molecular weights within a polymer are required in order to fully characterize it. The control of molecular weight and molecular weight distribution (MWD) is often used to obtain and improve certain desired physical properties in a polymer product.

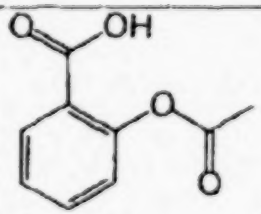
George Odian, *Principles of Polymerization*, pp. 22-23 (2nd Ed., John Wiley & Sons 1981) (Exhibit 3).

7. Table 1 (below) is shown as an example to contrast the difference between the true molecular weight and the apparent molecular weight by comparing aspirin and COP-1. A true molecular weight of a simple molecule chemical compound can be determined by summing the atomic weights of the atoms making up a molecule. Such molecular weight determination is based on the assumption that one can isolate a chemically pure compound and identify the exact chemical structure and know the identity of the atoms in the molecule (e.g., $C_9H_8O_4$ for aspirin in Table 1). In contrast, when the identity of the atoms making up a molecule cannot be determined, scientists use and report an apparent molecular weight. The apparent molecular weight is an experimental estimate of the true molecular weight determined using certain laboratory methods such as

ultracentrifugation, light scattering, and gel permeation chromatography (GPC) (also known as size exclusion chromatography (SEC) or gel filtration chromatography (GFC)).

8. As summarized in Table 1, the apparent molecular weight for COP-1 is different from the use of the true molecular weight for aspirin. Although the molecular weight of individual chains in COP-1 is defined by the following equation: 71.1 Da*A + 128.2 Da*L + 129.1 Da*G + 163.1 Da*T +18.0 Da, where G = L-glutamic acid, L = L-lysine, A = L-alanine, T = L-tyrosine, and Da = Daltons, the molecular weight of individual chains of COP-1 cannot be experimentally determined by counting the numbers of monomer units (i.e., G, L, A and T) in each polymer chain. Since COP-1 is a polydisperse mixture of peptide copolymer chains that contain different numbers of G, L, A and T, the apparent molecular weight of the individual COP-1 chains and the COP-1 molecular weight distribution have to be measured by experimental techniques such as GPC.

Table 1. True molecular weight and apparent molecular weight

Compound	Molecular structure	Molecular weight	Meanings of term "molecular weight"
Aspirin		180.2 Da (Molecular formula: $C_9H_8O_4$)	True molecular weight (Single

			value of molecular weight is sufficient and correct.)
COP-1	H-[G]g-[L]l-[A]a-[T]t-OH G = L-glutamic acid L = L-lysine A = L-alanine T = L-tyrosine g = No. of G in the chain l = No. of L in the chain a =No. of A in the chain t = No. of T in the chain	COP-1 exists as polydisperse mixtures of peptide copolymer chains that have different numbers of G, L, A and T amino acid units, and does not exist as a pure chemical compound with a single value of molecular weight. One has to employ experimental techniques	Apparent molecular weight (Molecular weight distribution (MWD) has to be characterized, from which different types average molecular weights has to be used to represent the mean and broadness of the MWD.)

		to estimate the molecular weight distribution of COP-1.	

9. The true molecular weight of a molecule may be determined by summing the atomic weights of the atoms making up that molecule only if the identity of the atoms making up the molecule is known. In the case of COP-1 in 1994, the identity of the atoms making up even a single COP-1 molecule was not known. Therefore, a scientist would not be able to determine the true molecular weight of a molecule of COP-1 in 1994. Additionally, the '808 patent does not mention anything about calculating the true molecular weight of COP-1 molecules.

10. The apparent molecular weight will closely approximate the true molecular weight only if the assumptions for the particular experimental method are satisfied. In the real world, it is often difficult to satisfy these assumptions, so often the apparent molecular weight may not closely approximate the true molecular weight.

11. I note that Teva's construction of the term "molecular weight" is inconsistent with the '808 patent. Teva seeks to construe "molecular weight" as a true molecular weight (Grant Declaration ¶ 63). However, a person of ordinary skill in the art, upon reading the '808 patent, would conclude the term "molecular weight" refers to an apparent molecular weight.

12. As stated in my First Expert Declaration (¶ 40), the '808 patent does describe how to estimate the apparent molecular weight of COP-1 molecules using GPC. Thus, "molecular weight" in the context of the '808 patent should be understood as an apparent molecular weight rather than a true molecular weight. Dr. Grant's definition of "molecular weight" does not apply to this case. Since apparent molecular weights are relative to the method of measurement, the definition needs to incorporate the use of GPC and the specific standards and conditions used in the analysis.

B. Claim phrases referring to copolymer-1 as a whole ("average molecular weight")

- **"copolymer-1 having a molecular weight" (not modified by "species of")**
- **"wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons "**
- **"copolymer-1 composition having an average molecular weight of about 4 to about 8.6 kDa "[23]**

13. I note that the figure legend in Figure 1 of the '808 patent reports average molecular weights of 7.7 kDa ("the 7.7 curve") and 12.0 kDa ("the 12.0 curve"). It is not specified in the patent which average molecular weight is being reported and the

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[23] These three example claim phrases refer to claim terms 12, 25, and 23 listed in the Joint Claim Construction Chart submitted on April 2, 2010.

prosecution histories provide no clarity to this issue (as discussed in my First Expert Declaration at ¶¶ 40-48).

14. A person of ordinary skill in 1994 would consider the term "average molecular weight" in the legend of Figure 1 to be referring to one of three averages commonly calculated using GPC. Those averages are number average molecular weight (Mn), weight average molecular weight (Mw), and z-average molecular weight (Mz). Table 2 has been provided to summarize the definition of those average molecular weights. Once the number fraction (N_i) or weight fraction (W_i) of the molecular weight distribution in known from GPC experiments, a person of ordinary skill in 1994 would use a personal computer and spreadsheet software, such as Microsoft Excel™, to calculate the different types of average molecular weights. These three definitions of average molecular weight and the equations for calculating them were well known in 1994.

Table 2. Typical average molecular weights calculated using GPC

Average molecular weight (MW)	Symbol	Definition from Ni	Definition from Wi
Number average MW	Mn (or $\overline{M}_n$)	$\frac{\sum_i N_i M_i}{\sum_i N_i}$	$\frac{\sum_i W_i}{\sum_i W_i / M_i}$

Weight average MW	$\overline{\text{Mw}}$ (or Mw)	$\frac{\sum_i N_i M_i^2}{\sum_i N_i M_i}$	$\frac{\sum_i W_i M_i}{\sum_i W_i}$
z-average MW	Mz (or $\overline{M}$ z)	$\frac{\sum_i N_i M_i^3}{\sum_i N_i M_i^3}$	$\frac{\sum_i W_i M_i^2}{\sum_i W_i M_i}$

1. Average Molecular Weights and Peak Molecular Weight.

15. Furthermore, Dr. Grant states that a person of ordinary skill in the art would understand the term "average molecular weight" to be "peak molecular weight" (Grant Declaration ¶70). I disagree for several reasons.

16. In 1994, the peak molecular weight (Mp) may be used to describe the molecular weight distributions from GPC experiments. However, as discussed further below, the peak molecular weight as defined by the peak corresponding to Figure 1 in the '808 patent is not technically an averaged quantity. Therefore, a person of ordinary skill seeing the figure legend of "average molecular weight" simply would not think of Mp.

17. But even if a person of ordinary skill were to check to see if the "average molecular weights" referred to in the Figure 1 legend are Mp values,

such person would immediately see that the peaks of curves provided for the 7.7 kDa and 12.0 kDa samples do not align with the molecular weights of 7.7 kDa and 12.0 on the x-axis. See Figure 1 below. Therefore, a person of ordinary skill in the art would conclude that the average molecular weights referred to in the figure legend cannot be Mp values.

Figure 1. The Figure 1 legend in the '808 patent does not report Mp. Figure 1 of the '808 patent was modified to include arrows corresponding to 7.7kDa and 12.0 kDa on the x-axis.

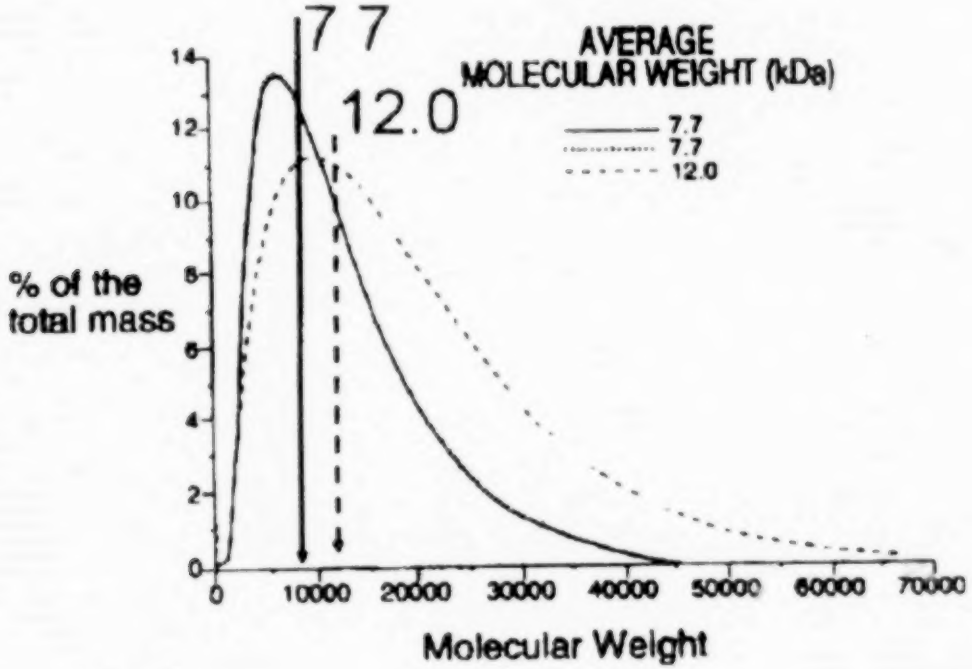


FIG. 1

18. Dr. Grant states that a person of ordinary skill in the art would assume the peak would have been expected to shift slightly from the value read from the peak of the chromatogram (Grant Declaration ¶ 52). I disagree. The peak would only be expected to shift if there was a small number of data points

collected for each of these curves. The curves in the '808 patent are continuous, suggesting to the person of ordinary skill that many data points were collected. Furthermore, the '808 patent and prosecution histories say nothing about the number of data points underlying the curves in Figure 1. For these reasons, a person of ordinary skill in the art would assume that enough data points were collected so that no shift in the peak would be expected. Moreover, even if one of ordinary skill were to wonder whether the curves had been shifted, he or she would have no way of knowing in which direction they would have been shifted or the magnitude of the shift.

19. In fact, whether or not a person of ordinary skill would have checked the Mp values for the curves in Figure 1, he or she certainly would have calculated Mn, Mw, and Mz for both the 7.7 curve and the 12.0 curve to determine if any of these values matched the values reported in the Figure 1 legend because these were and still are the commonly used "average molecular weights." Calculating each of these averages was routine and well within the skill of a person of ordinary skill in the art in 1994.

20. To calculate Mn, Mw, and Mz for the Figure 1 curves, a person of ordinary skill in the art would collect nearly evenly-spaced (x,y) data points for each curve. This could have been accomplished in 1994 by enlarging the Figure 1 image and using graph paper to collect many data points along each of the curves. This easily could have been done in 1994. A person of ordinary skill in the art would know that the more

data points collected, the better the representation of the curves shown in Figure 1.

21. Alternatively, a person of ordinary skill in 1994 could have used a personal computer and graph digitizing software such as the software program "UN-SCAN-IT" from www.silkscientific.com. This digitizing software has been available since 1992 (see http://www.silkscientific.com/about/index.htm). This software is affordable, easy to use for graph digitizing, and reliable enough to be used in many scientific journals. (For details, please see www.silkscientific.com.) In the following outline, I have described the exact procedure to obtain (x,y) data points from the curves in Figure 1 of the '808 patent.

Outline 1. Digitizing the curves in Figure 1 of the '808 patent

Step 1: Read '808 patent Step 1: Read '808 patent and make a digital image file from Figure 1 of the patent.

(1) Read the pdf file of 808 patent using Adobe Acrobat software

(2) Screen capture using "Print screen" of window software after setting the pdf zoom of "170%"

(3) Using "painter" program in the accessory of window software, capture the print screen image into the image file in the format of BMP file.

(4) Using Adobe "Photoshop" program open the BMP file and convert the image into "Gray scale",

because the screen captured image is in "RGB color mode." Using Adobe "Photoshop" program, the gray scale image file is save as a TIFF image file.

Step 2: Select either 7.7 KDa or 12.0 kDa curve in Figure 1 for the digitization of data.

(5) Using "Eraser", remove the other curves and leave only one curve that you would like to analyze. Use Zoom-in function to make sure that you are not deleting the curve of your interest when you use the eraser function in Adobe Photoshop software.

A. **"solid-line 7.7 kDa in Figure 1" -**

i. Original Pixel dimension 1267*910 pixels (17.6width* 12.6 height inches at **72 pixels/inch**) (image size ~ 1.1 MB)

ii. Leaved the solid line (removed the dotted features in "dotted 7.7 kDa sample")

B. **"Dotted 12.0 kDa sample in Figure 1"**

i. riginal Pixel dimension 1267*910 pixels (7.6width* 12.6 height inches at **72 pixels/inch**) (image size ~ 1.1 MB)

ii. It is important to note that the data points had been added manually using Adobe Photoshop to perform the data interpolation between two dotted points/segments in the "dotted 12.0 kD Curve" Now the new image file has been made to "**solid-line 12.0kDa sample**." This is better estimation to reduce the potential errors in digitizing the data. The Plot change has been

compared before and after to ensure that we are correctly performing the data interpolation.

Step 3: Obtain (x,y) data using digitizing software, such as "UN-SCAN-IT Digitize software"

(6) Start "UN-SCAN-IT Digitize software" and open the image files prepared in step 2.

i. Choose "Standard Line" for the "solid-line 7.7 kDa curve."

1. Set up method Drag and Drop/Color type Gray scale (intensity width 25), scale linear /**Line side Both surfaces (Mid-line)**/Grid Line Filter None, Line Flow Direction >> Left to Right >> / Line Follow Algorithm non-sloped/ digitizing speed "3". Correct for the image tilting "Yes"

2. Data Point Acquisition Resolution and No. of Data Points (Followings are shown as examples of data points obtained)

A. Digitizing resolution "2 scanner unit" Total (x,y) about 338 digitized points

B. Digitizing resolution "3 scanner unit" Total (x,y) about 226 digitized points

C. Digitizing resolution "4 scanner unit" Total (x,y) about 169 digitized points

ii. Choose "Standard Line for the "dotted line 12.0 kDa curve" that had been converted to "solid-line 12.0 kDa curve" as previously described

1. Set up method Drag and Drop/Color type Gray scale (intensity width 25), scale linear /**Line side - Both surfaces (Mid-line)**/Grid Line Filter None, Line Flow Direction >> Left to Right >> / Line Follow Algorithm non-sloped/ digitizing speed "3". Correct for the image tilting "Yes"

2. Data Point Acquisition Resolution and No. of Data Points (Followings are shown as examples of data points obtained.)

A. Digitizing resolution "2 scanner unit" Total (x,y) about 506 digitized points

B. Digitizing resolution "3 scanner unit" Total (x,y) about 338 digitized points

22. Having these (x,y) data points for each of the curves in Figure 1, a person of ordinary skill in the art would normalize these values to either the total area under each curve or to the total height of each curve depending on how Figure 1 was generated. The patent is silent on whether a person of ordinary skill in the art should normalize to the total area or total height of the curves. However, I note Dr. Grant in his declaration (Grant Declaration ¶¶ 48-51) indicates one would normalize based on the total height of the curves. I have thus based my calculations on this assumption.

23. Having the normalized (x,y) data points for each of the curves in Figure 1, a person of ordinary skill in the art would calculate Mn, Mw, and Mz using the equations outlined in Table 2. I have completed this analysis for the 7.7 curve using

spreadsheet software such as Microsoft Excel™, just as one of ordinary skill would have done either by hand or computer software in 1994. Assuming that a person of ordinary skill would have chosen at least 100 data points in order to have a reasonable degree of certainty in the results, the results of the analysis that such a person would have obtained are shown in the following table (Table 3). (The numbers of data points shown in Table 3 are based on the way that the computer program picks evenly spaced data points along the curve.)

Table 3. Molecular weight averages for the 7.7 curve in Figure 1 of the '808 patent

No. of Data Points	Mn	Mw	Ml	PD	Mp
338	8.7 kDa	12.9 kDa	17.6 kDa	1 48	6.6 ± 0.2 kDa
226	8.7 kDa	12.9 kDa	17.6 kDa	1.48	6.6 ± 0.2 kDa
169	8.7 kDa	12.9 kDa	17.6 kDa	1.48	6.7 ± 0. 3 kDa
113	8.7 kDa	12.9 kDa	17.6 kDa	1.48	6.8 ± 0.7 kDa

24. As shown in Table 3, using sufficient numbers of data points will yield relatively constant values for Mn, Mw, Mz of 8.7 kDa, 12.9 kDa, and 17.6 kDa, respectively. The Mp values were obtained by plotting the digitized data points in plotting software with grid options to visually estimate the highest y-

axis data point. The error in peak molecular weight (Mp) was estimated visually by taking the ranges of the molecular weights that included the approximately second largest y-axis value. A person of ordinary skill would understand that the Mp value of approximately 6.6 kDa does not correspond to the value one observes for the 7.7 curve in the Figure 1 legend of the '808 patent. The 7.7 kDa value sits almost evenly between Mp and Mn. Upon seeing these values, a person of ordinary skill in the art would conclude that none of these values (i.e., 8.7 kDa, 12.9 kDa, 17.6 kDa, and 6.6 kDa for Mn, Mw, Mz, and Mp) match the 7.7 kDa reported in the '808 patent Figure 1 legend, and so he or she would have next looked at the average molecular weight values obtained from the 12.0 kDa curve shown in Figure 1.

25. Accordingly, I performed the same analysis for the 12.0 curve as described above for the 7.7 curve. These results are shown in the following table (Table 4).

Table 4. Molecular weight averages for the 12.0 curve in Figure 1 of the '808 patent

No. of Data Points	Mn	Mw	Ml	PD	Mp
506	12.1 kDa	19.7 kDa	27.6 kDa	1.63	10.1 ± 0.4 kDa
338	12.1 kDa	19.7 kDa	27.6 kDa	1.63	10.0 ± 0.4 kDa

253	12.1 kDa	19.7 kDa	27.6 kDa	1.63	10.0 ± 0.8 kDa
127	12.1 kDa	19.7 kDa	27.6 kDa	1.63	10.0 ± 0.8 kDa

The values for Mn, Mw, Mz, and Mp are 12.1 kDa, 19.7 kDa, 27.6 kDa, and approximately 10.0 kDa respectively. A person of ordinary skill in the art upon seeing these values would likely conclude that the 12.0 kDa in the '808 patent Figure 1 legend refers to Mn, and thus the 7.7 kDa also was likely meant to refer to Mn.

26. In addition, a person of ordinary skill would be aware of Paul Flory's (1974 Nobel Prize in Chemistry) famous textbook "Principles of Polymer Chemistry (1953)" The following excerpt from "Principles of Polymer Chemistry (1953)" suggests when the term "average molecular weight" is not clearly specified, number average molecular weight (Mn) should be understood.

> It is sufficient to mention here that the hazards of ambiguity can be avoided by referring to the *average* degree of polymerization, provided that the manner of averaging is specified. Unless stated otherwise, the term *average degree of polymerization* refers to the ordinary average (*number average*, see Chap. VII) obtained by dividing the total number of structural units by the total number of molecules. Similarly, the *average molecular weight* (more accurately, the *number average molecular weight*) represents the

> mass of the sample divided by the number of moles it contains. Where no confusion is likely to arise, the qualifying adjective *average* may be omitted. Implicit in all discussions of polymer phenomena, however, must be recognition of their inherent molecular heterogeneity.

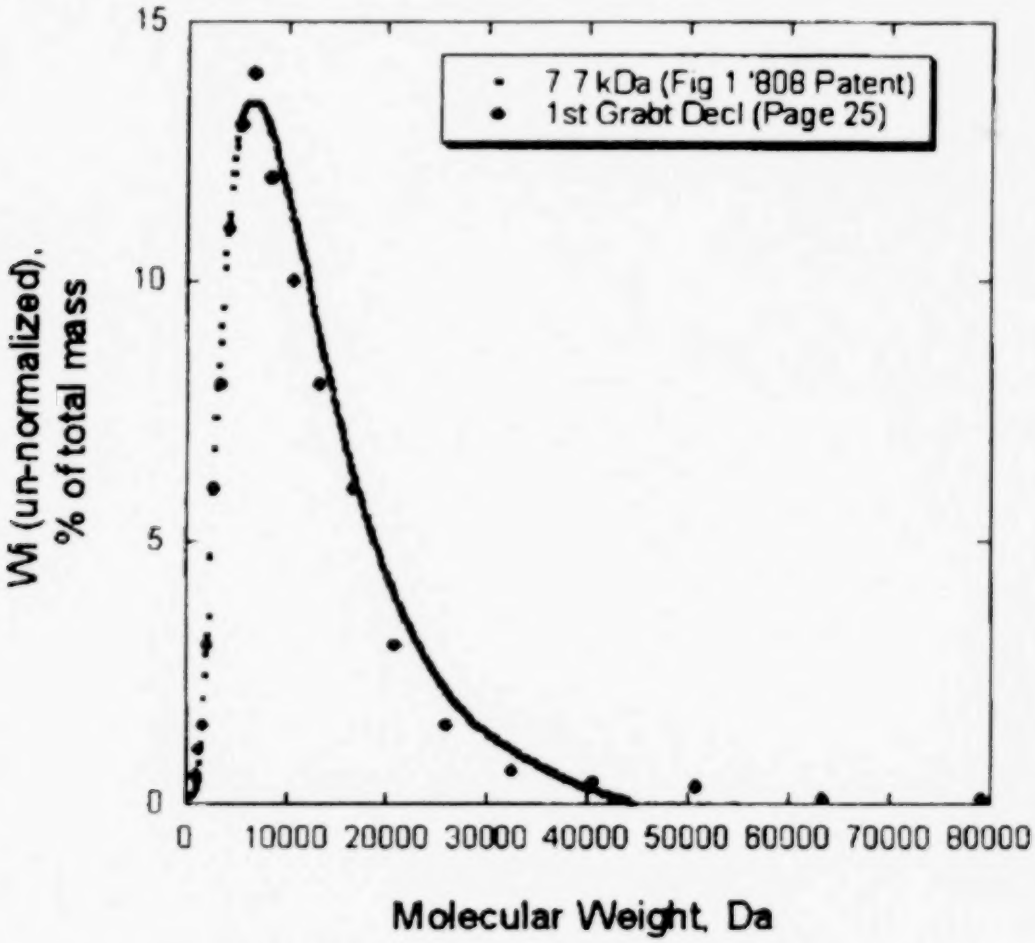
Pages 35-36, "Principles of Polymerization" by Paul Flory (1953) Cornell University Press. (Exhibit 4). Dr. Grant also cited this text in his first declaration (Grant Declaration ¶ 69).

27. Additionally, I note from my calculations, that Mp < Mn < Mw < Mz for the 7.7 and 12.0 curves shown in Figure 1 of the '808 patent. This fact argues against the presumption that "Mn typically is smaller than Mp" made by Dr. Grant in his first declaration (Grant Declaration ¶ 73). Although Dr. Grant's statement may be true for many polymers, it is not true for the batches of COP-1 in Figure 1 and likely will not be true for other batches of COP-1 having asymmetric distribution curves like those shown in Figure 1 of the '808 patent. While it is always true that Mn < Mw < Mz for polydisperse polymers, the location of peak molecular weight (Mp) strongly depends of the broadness and symmetry of the molecular weight distribution around the peak.

28. I also note that the sample GPC data submitted by Dr. Grant in his first declaration (Grant Declaration ¶¶ 50-51) does not accurately depict the 7.7 curve in Figure 1 of the '808 patent. As seen in the following figure (Figure 2), Dr. Grant's data points do not accurately superimpose onto my digitized data from the 7.7 curve. Notably, Dr.

Grant's data contains data points above 50 kDa which are not represented in the 7.7 curve in Figure 1 of the '808 patent.

Figure 2. Dr. Grant's data points do not accurately depict the 7.7 curve. My digitized data represented here contains 338 data points (small red dots). Dr. Grant's data contains 20 data points (large blue circles).



C. Defining peak molecular weight as an "average molecular weight" or a "mode" is scientifically incorrect.

29. The peak molecular weight corresponding to Figure 1 of the '808 patent is not, technically speaking, an average molecular weight. And contrary to what Dr. Grant states, the peak of Figure 1 is clearly not a "mode."

30. Upon reviewing the Grant Declaration, it is not clear whether he has defined peak molecular weight to mean the peaks shown in Figure 1 or the peaks shown in Figure 2. I note that Dr. Grant states in his first declaration (Grant Declaration ¶ 72 footnote 14) that peak molecular weight corresponds "to the peak of a mass fraction vs. molecular weight curve, such as those in Figure 1." This was the accepted definition of Mp in 1994 and it is still the accepted definition used today. However, in the Grant Declaration (¶ 71), Dr. Grant states that peak molecular weight is an average molecular weight by stating the peak in Figure 1 is also a "mode." Dr. Grant cites no authority for this statement and in fact it is plainly incorrect and contrary to common knowledge in the art in 1994. The peak of Figure 1 is clearly not the "mode" of the batches of COP-1 shown. Rather, as discussed below, the "mode" can only be derived from Figure 2.

31. A "mode" is a well-defined term in mathematics. The "mode" of a set of data is the value in a set that can be counted and occurs most often or frequently. The question is then whether the peaks of the curves in Figure 1 represent the modes of those batches of COP-1. In other words, do the peaks in Figure 1 correspond to the molecular weight that occurs most often in a batch of COP-1. The simple

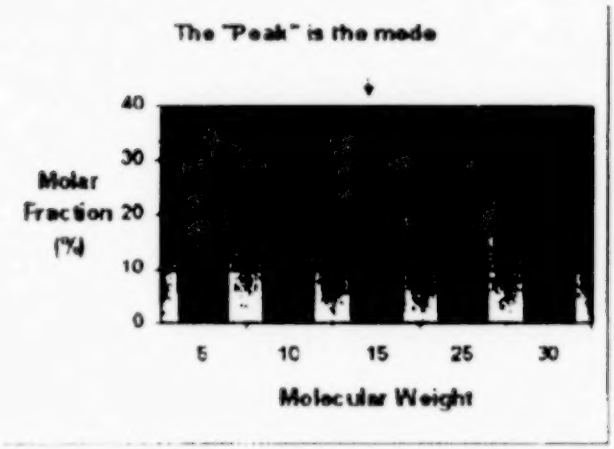
answer is "no." To answer that question, one must instead look to Figure 2.

32. Figure 2 plots the % molar fraction on the y axis versus molecular weight on the x axis. To determine "the most frequent value of molecular weight that represents the general significance of a set of unequal individual molecular weights of species within a sample" (Grant Declaration ¶ 71) or "mode" of the COP-1 sample, a person of ordinary skill would determine the molecular weight value associated with the greatest number of molecules. This value of molecular weight can be determined for a polymer sample if one is given the molecular weight distribution (MWD) curve on a molar fraction basis. In other words, if a person of ordinary skill has the MWD information based on the number of molecules as a function of molecular weight (This corresponds to Figure 2, not Figure 1), he/she will look for the value of molecular weight that exhibits the largest number of molecules on the MWD curve. Therefore, it is certain that this value of molecular weight is the "peak" of the curves shown in Figure 2. Unlike Figure 2, Figure 1 plots the % total mass on the y axis versus molecular weight on the x axis. Because the y-axis value of mass % is proportional to the product of (the number of molecules) * (molecular weight), one cannot find the highest number of molecules from the values of the y-axis estimated from Figure 1. The peaks on these curves represent the molecular weight associated with the greatest percentage of mass not the greatest percentage with respect to the number of molecules. Since in this case the molecular weight associated with the greatest percentage of mass does not indicate the

molecular weight associated with the greatest percentage of molecules, the Peaks shown in Figure 1 cannot represent the mode.

33. A simple example illustrates this point. Consider a data set containing 8 molecules with the following molecular weights (in kDa) [5, 10, 15, 15, 15, 25, 25, 30]. A person of ordinary skill would find that the mode of this data set is 15 because 15 occurs more frequently than any other molecular weight. A person of ordinary skill could easily plot this data similar to Figure 2 in the '808 patent. The figure would look like figure 3 below.

Figure 3. Plot of Molar Fraction (%) vs. molecular weight

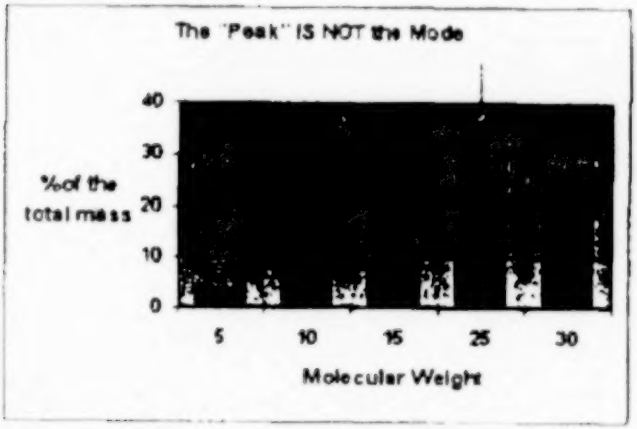


5	1	12.5
10	1	12.5
15	3	37.5
25	2	25
30	1	12.5

It is clear that the peak in this plot corresponds to the mode which is 15 kDa.

34. The person of ordinary skill could also plot this same data similar to Figure 1 in the '808 patent. The figure would look like figure 4 below.

Figure 4. Plot of % of the total mass vs. molecular weight



5	5	3.57
10	10	7.14
15	45	32.14
25	50	35.71
30	30	21.43

The peak in this figure is at 25 kDa. As this simple example illustrates, the peak of the second plot does not correspond to the mode of that data set. Therefore, if one uses the molecular weight distribution plotting the % of the total mass as a function of molecular weight this will lead to an incorrect estimation for the value of the mode. That is because even though there are fewer molecules having a molecular weight of 25 kDa, they collectively account for a greater percentage of the mass than the more abundant 15 kDa molecules. Like the second plot in this simple example, the peaks in Figure 1 are not modes and thus should not be considered averages.

35. I note that the peaks in Figure 2, from which the mode of the 7.7 kDa curve and 12.0 kDa curves properly could be derived, are nearly the same, i.e., around 4-5 kDa.

I declare under penalty of perjury that the factual statements contained herein are known by me or believed by me to be correct.

Dated this 21st day of May, 2010.

_____

Chang Ryu, Ph.D.

[EXHIBITS 1-4 OMITTED]

[Exhibit 42 to the Declaration of Joseph B. Crystal]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., et al.,	)	
Plaintiffs,	)	
v.	)	Civil Action No.
MYLAN PHARMACEUTICALS, INC., et al.,	)	09-CV-8824 (BSJ)(AJP)
Defendants.	)	

CONFIDENTIAL

Videotaped Deposition of
CHANG YEOL RYU, Ph.D.

Washington, DC

Tuesday, June 22, 2010

9:09 a.m.

* * *

[26]

* * *

A Okay. Undergrad course, I use Joung and Lovell.

Q Can you spell that, please? A J-O-U-N-G. Other one is L-O-V-E-L-L. The title of the textbook -- I just remember the colors, okay? It's in my textbook -- I don't -- actually I don't have to remember, because it's in my office. But that's the textbook I used for undergrad.

Q And for your graduate course?

A Graduate course, it is a textbook written by Hiemenz, H-I-E-M-E-N-Z. And Lodge, L-O-D-G-E. I like to add on the other textbook that is important, which is called Cowie, C-O-W-I-E. That's a textbook that I also use for undergrad course. And there are -- I taught different polymer courses for graduate. The other courses that I use is -- textbook is "Polymer HPLC," by Pasch, P-A-S-C-H. And the other one is a European, which is very difficult names. Pasch is the one that I know.

Q With respect to molecular weight analysis?

A Yes.

Q For undergraduate or graduate courses, [27] which textbooks do you use?

A "Molecular Weight Analysis." Those textbooks are being used.

Q The ones you just named, Joung and Lovell, Hiemenz and Lodge, Cowie, and the book by Pasch, "Polymer HPLC"?

A Those are the textbooks -- "Polymer HPLC" is more about HPLC characterization of polymers. And other textbooks contains that polymer molecular weight analysis techniques that has been described.

Q What is HPLC?

A HPLC is a type of liquid chromatography. It stands for high performance liquid chromatography.

Q Was HPLC ever referred to as high pressure liquid chromatography?

A Some people use that term, as a high pressure liquid chromatography, too. But it is typically -- that term is mixed use.

Q Is size exclusion chromatography a type of HPLC?

A Yes. Type of HPLC.

[28]

Q Just so we can be on the same page today, gel permeation chromatography, can you tell me what that is?

A Gel permeation chromatography is a technique first suggested by the group in Sweden, in paper in their Nature, 1959. They published a paper on gel filtration for protein purification.

Q Did you say "gel filtration" or "gel permeation"?

A Gel filtration, for 1959. And gel permeation was later coined by the person named John Moore from Dow Chemical.

Q John Moore?

A John Moore, yes, a common last name, in 1964. That was the first paper that coin the term "gel permeation chromatography," using organic solvent to characterize synthetic polymer that has distribution of molecular weight.

Q Gel filtration chromatography is referred to as GFC?

A Gel filtration chromatography refers to GFC.

[29]

Q Gel permeation chromatography is GPC?

A GPC.

Q And GPC and GFC are types of size exclusion chromatography?

A It is a same -- it is a term that people mix -- use the term depending on who you aretalking to.

Q For the purposes of the deposition today, if I refer to size exclusion chromatography or SEC, will you understand that to include GPC and GFC?

A I will understand that, yes.

Q You mentioned that the group in Sweden in 1959 had developed gel filtration chromatography or had published a paper on gel filtration chromatography to separate proteins; is that right?

A Yes.

Q Is that aqueous separation?

A That is using the aqueous as a mobile phase.

Q What does that mean, to use aqueous separation?

A Aqueous phase means the mobile phase

* * *

[54]

* * *

frame, 1993, 1994?

A I do not have a characterization of polypeptide. But I certainly -- it's very important for me to understand the characterization of polydispersed polypeptides.

Q In Dr. Lodge's lab, was any research being done on the use of aqueous size exclusion chromatography?

A We are focusing on using nonaqueous GPC system. So we do not have -- in Dr. Lodge's lab we do not have a GPC or GFC using aqueous solvent.

Q Doctor, what year did you receive your Ph.D.?

A 1998.

Q What was the subject matter of your thesis?

A The title of my thesis is "Structure and Dynamics of Block Copolymer Melts and Solution."

Q Doctor, at any point in your career have you done research using aqueous size exclusion chromatography?

A In -- recently I start to interested in [55] doing aqueous GPC system, aqueous GPC system. But

that's just an initial attempt for my faculty career. I was focussing on characterizing polydispersed synthetic polymer sample using GPC.

Q When you say "recently," you've begun to research aqueous size exclusion chromatographyhow recently?

A That would be a few months ago.

Q Do you have an aqueous size exclusion chromatography analytical device, for lack of a better term, in your laboratory?

A In my laboratory we -- actually my students are still struggling to put that instrument together. We are making the GPC. GPC is a term -- like I said, it is a type of HPLC equipment. So you need components of HPLC. And what simply means a GPC or aqueous GPC means your mobile phase, biophase, mobile phase, is a water-based system. And it has its own challenges compared to organic polymer system. That is actually why I tried to stay away from the aqueous GPC system, because there is a [56] very -- just is very difficult.

Q I'm sorry, I didn't mean to cut you off. You had something else to say? Were you finished?

A Yes, I'm finished. 10:15:03

Q At any point in your career, Doctor, have you studied molecular weight determinations of polypeptides? 10:15:12

A That specific polymer, I don't have research. But I can certainly -- the subject that is relevant to the characterization of molecular weight distributions and molecular weight is really -- is not

a question about whether it is a copolymer-1 or not. It is a question about a polymer that is a distribution of molecular weights.

MR. JAMES: Why don't we take a five-minute break.

THE VIDEOGRAPHER: We're going off the record. The time is 10:15 a.m.

(Recess.)

THE VIDEOGRAPHER: We are back on the record. The time is 10:30 a.m.

BY MR. JAMES:

[57]

Q Dr. Ryu, you mentioned that in your laboratory, your laboratory that you run now --

A Yes.

Q -- you have the ability to do size exclusion chromatography.

A Yes.

Q And size exclusion chromatography is an analytical technique that separates molecules on the basis of their hydrodynamic size, correct?

A We would like to use the term "hydrodynamic volume."

Q Okay. Who is "we"?

A "We" means polymer chemists, including myself.

Q And why hydrodynamic volume as opposed to hydrodynamic size?

A "Hydrodynamic volume" and "size" is an interchangeable term. But what has been suggested by Flory-Fox equation was what GPC is really governed by hydrodynamic volume. Essentially, if you understand the volume versus lengths or size, it's just a cube-dependent term. It's just a matter

* * *

[78]

* * *

You need to have a calibration curve to convert the retention time into the molecular weight of the sample.

Q And the retention time is linearly related to the log of the molecular weight of the polymers as they exit the column, correct?

A That's not true.

Q That's not true?

A It's not true.

Q Why is that not true?

A In principle, it has been taught as a simplified -- because of the real nature of the column, the theoretical foundation for linearity comes from the -- I guess the assumption based on the hydrodynamic volume. But the column itself has a limitation of molecular weight ranges is limited. There is a window of molecular weight that can do some pseudo-linear behaviors. And so you cannot really do the linear fit. That's a wrong way to do SEC. And the way that you typically do – actually we are doing it in our lab most of the [79] time, is what we call the

more high order fit. It's called a cubic – cubic or even the fifth order of fit, to naturally find out calibration curve. In other words, we don't call calibration line, we call calibration curve, because of the real nature of this curve. Each column is actually -- is different. It's like -- we call it "has its own personality" for giving the separation.

Q When you say there is a cubic or a fifth order fit --

A Yes.

Q -- what is the fit between?

A So I would say log molecular weight is a function of power law of retention volume or retention time.

Q I'm sorry, I missed the middle part of that. Did you say "power law"?

A Power law, which means you can use -- for example, log molecular weight equals A plus PX plus CX squared plus DX cubed. And then X means retention volume or retention time. And then once [80] you have these data points of the relationship between retention time and the molecular weight of calibration standard, which is a well-defined molecular weight with a narrow molecular weight distribution, and then you can use that information to get calibration curve. With the mathematical formula that you get, you can use.

Q The calibration curve correlates the retention time or the retention volume with the log molecular weight, correct?

A With tension volume, with log molecular weight, yes. So it is related --

Q Whether it's a line or a third order polynomial or a fifth order polynomial, or a cubic relationship, the relationship is between retention time or volume and log molecular weight; is that right?

MR. WHITE: Asked and answered.

THE WITNESS: It is related. There is -- like we -- like I said before, the higher the molecular weight it is, the faster it -- [inaudible].

[81]

(The reporter asked for clarification.)

A The polymers are coming out. The shorter retention time, the lower the molecular weight, the longer it takes to come out. Retention time is higher.

Q In 1994, was online viscometry available?

A Online viscometry, yes. I'm not so sure -- I am aware of what is called a triple detector. It is the detector that use light scattering refractive index and online viscometry together. I have to look at the literature, whether that was available.

Q In 1994, did the person of skill in the art have the ability to measure the intrinsic viscosity of polymers?

A Yes. So there is a distinction between measuring the intrinsic viscosity using capillary glassware versus online detector.

Q Yes. I'm asking about the former.

A Yes. That one, people do know how to measure the intrinsic viscosity.

Q In 1994?

A 1994.

[82]

Q In 1994, was it known that in order to have an accurate molecular weight determination using size exclusion chromatography, that you needed calibration standards that had a similar relationship between hydrodynamic size and molecular weight as the sample you were measuring?

MR. WHITE: Objection to form.

THE WITNESS: So the calibration standard should have -- there is a lot of I guess requirements has to come in to really define whether the GPC give you molecular weight in terms of -- the molecular weight from the GPC is really -- depends on the quality of the standard, of GPC calibration standard. One of the requirements will be the one that they should have the same chain conformation relationship. Chain conformation has to be similar as those in the calibration standards. And the sample of interest should have same kind of chain conformation. And the relationship between the molecular weight and the hydrodynamic volume are [83] similar. And that is -- that is one of the requirements to -- it has fidelity of the GPC characterization.

BY MR. JAMES:

Q And that was known in 1994, correct?

A So what do you mean by "that was known"?

Q The characteristics of the calibration standards that you just outlined. Those characteristics were well understood in 1994, correct?

A So the -- what I'm referring to is the characteristic of any kinds of GPC standards should have a characteristic of sample of interest. It's a characteristic -- it is -- when that is -- actually I find it is a difficult question when you come with polymers called polypeptide with such a -- four different monomers. And that -- because a peptide, I know from my biochemistry book, it has a secondary structure such as possibly can have a beta sheet and alpha helixes.

(The reporter asked for clarification.)

[84]

A Alpha helixes. That's a term that -- secondary structures in the many peptides. Whereas the polymer that I am very familiar with characterizing is a synthetic polymer, is typically well-dissolved in an organic solvent so we can comfortably use that polymer and other polymer standard that has a similar characteristics.

Q Do you believe that the person of skill in the art in 1994 would have had experience inaqueous size exclusion chromatography?

MR. WHITE: Objection to form. You can answer.

THE WITNESS: "Experience" means that they understand the result and -- yes, they would understand how to interpret it, the result of the GPC.

BY MR. JAMES:

Q Do you believe the person of skill in the art in 1994 would have had experience doing research on molecular weight analysis of synthetic peptides?

A So --

MR. WHITE: Objection to form.

[85]

THE WITNESS: If you are referring the research is including the reading literatures, certainly yes, they understand what it means when you are looking at the data, they understand that.

BY MR. JAMES:

Q But that's not the way you defined "research" at the beginning of the day, correct?

A I didn't know how I want to define my -- the research I would like to define when I talk to my colleagues with my graduate students, is how I define researches. But also research means something that you study and search with hands-on experience, and also looking at literatures and textbooks, all kinds of understanding to enhance your knowledges [sic], is all contribute to the research.

Q So your definition of research includes both hands-on experience and also simply readingthe literature?

A I would say yes. I agree with you. You need -- those are the components of those.

Q In 1994, would a person of skill in the

* * *

[242]

* * *

looking at the manual.

Q I understand that.

A And --

Q I'm asking you if you know.

A I have to -- I don't remember the details about the condition, to what level has been given.

Q And you don't have experience in aqueous size exclusion chromatography, correct? You've never done aqueous size exclusion chromatography in your entire career, correct?

MR. WHITE: Objection to form.

THE WITNESS: That's not correct. I said my lab started to do aqueous GPC --

BY MR. JAMES:

Q A few months ago.

A -- a few months ago, and that we start to see whole kinds of problems compared to the organic solvent. This is exactly the reason that I tried to stay away from working on this aqueous GPC, because aqueous GPC, there's so many different factors,

charges, pHs, temperatures, ionic strength,compared to the GPC that I had been dealing withover the [243] more than ten years of my research career,15, 20 years for my research career, working on the synthetic polymer. It is a neutral polymer, it is a random polymer that is a random copolymer random coil. Even for that we are still struggling, what about your chemical identity, calibration standards, your sample of interest are different. So because of that I actually -- I try not to work on this field. The reason I recently start to work on it is actually not because of this case. My colleagues in the chemical engineering department has a sample of an interest. And actually my student worked on the system, and he already complained that there is another very practical issue working on the aqueous GPC, for example they say the pump starts to get corroded because of the salt in the water. We don't have that problem with the solvent. We have different kinds of problem, it will be damp, there will be ruptures. I don't have that problem with dampness or rupture, because -- but there's another whole kind of problems I have to [244] facing it. Then there is detection problems. So this is why I try to essentially, in a way, stay away from to use an aqueous GPC to characterize some sample. But certainly the understanding of the polydispersity, the definition of average molecular weight, and how -- what are the uncertainties. If by using the size extrusion chromatography, using light scattering, ultracentrifuge, osmometry measurement, those are the different kinds of experimental means, as a synthetic polymer chemist who is constantly dealing with the polymer sample with a polydispersed

molecular weight distribution, these are the samples that we have to analyze with. We understand there is -- assumptions are being made to lead to the numbers that we can get as a molecular weight, which is -- like I said, is an apparent molecular weight, it's not a true molecular weight, which is -- we don't really know.

Q Dr. Ryu, in any of your papers in your career, have you ever listed the age of the column as a condition?

[245]

A This is --

Q That's a yes-or-no question. Have you ever listed the age of the column in a single paper that you have published?

A So I would like to say no to that question. But what we do in the lab is, we keep track of how long the column has been used, so we can decide when the column has been calibrated and when is about the time to replace a new column. This is one of the internal regulations as to the person working on GPC to keep track of. And your responsibility as a scientist is to present the result that will be -- this is an experimental conditions that you have to consider to give to the best of your knowledge, this is the result that I can present. So I don't list the age of my column in my publications, no.

Q If you look at paragraph 29, please, in your first declaration. Do you see that paragraph? It addresses the topic of peak molecular weight. you see that, Dr. Ryu?

A So paragraph 20?

* * *

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD., *Plaintiffs,* v. MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD., *Defendants.*	Civil Action No. 09-CV-8824 (BSJ) (AJP) **FILED UNDER SEAL**

THIRD DECLARATION OF CHANG RYU, Ph.D.

1. I have been retained by Perkins Coie LLP to provide my opinions as an expert witness on behalf of Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (collectively, "Defendants") regarding certain issues that pertain to U.S. Patents Nos. 5,800,808 ("the '808 patent"), 5,981,589 ("the '589 patent"), 6,048,898 ("the '898 patent"), 6,054,430 ("the '430 patent"), 6,342,476 ("the '476 patent"), 6,362,161 ("the '161 patent"), 6,620,847 ("the '847 patent"), 6,939,539 ("the '539 patent"), and 7,199,098

("the '098 patent"). I will refer to these patents collectively as "the '808 patent" unless indicated otherwise. I previously submitted two expert witness declarations dated April 20, 2010 ("First Expert Declaration") and May 21, 2010 ("Second Expert Declaration"). I now submit the following additional expert witness declaration on behalf of Defendants.

I. EDUCATION AND EXPERIENCE

2. My qualifications are described in my First Expert Declaration, which I incorporate herein by reference. I am currently an Associate Professor in the Department of Chemistry and Chemical Biology at the Rennsselaer Polytechnic Institute ("RPI") in Troy, New York. I am also a faculty member of New York State Center for Polymer Synthesis and National Science Foundation Nanoscale Science and Engineering Center. For the last twenty years, my research has utilized size exclusion chromatography (SEC) for the analysis of synthetic homopolymers and copolymers that have polydisperse molecular weight distributions. A copy of my curriculum vitae, which lists my publications and describes my qualifications in detail, is attached as Exhibit 1 to my First Expert Declaration.

II. ASSIGNMENT

3. I have been tasked by Defendants to analyze, review and consider the opinions stated in the Declaration of Gregory A. Grant, Ph.D. dated April 19, 2010 ("First Grant Declaration"), the Declaration of Gregory A. Grant, Ph.D. dated May 20, 2010 ("Second Grant Declaration"), and the Declaration of Paul L. Dubin, Ph.D. dated May 21, 2010 ("Dubin

Declaration"), which were submitted on behalf of Teva Pharmaceutical USA Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience Inc., and Yeda Research and Development Co. Ltd. (collectively, "Plaintiffs").

4. I have reviewed the First Grant Declaration, the Second Grant Declaration, and the Dubin Declaration and considered the opinions stated within those declarations. In response to those declarations, I now provide the following additional opinions. In formulating my opinions, I have also considered the '808 patent (Exhibit 2 in my First Expert Declaration) and prosecution histories of the patents-in-suit. A detailed list of the materials I have reviewed in preparation of this third declaration is attached as Exhibit 1.

III. STATEMENT OF OPINIONS AND BASES IN SUPPORT

5. Meaningful comparisons of the molecular weight distributions of two copolymer-1 samples was not possible in 1994 without knowing that the calibration standards and SEC running conditions were the same for both samples.

6. Whether a molecular weight distribution determined using SEC is described using an average molecular weight (AMW) or is described using a percentage of the molecules in a specified molecular weight range (as both used in the Teva patents), the results can change significantly depending on which SEC calibration standards and running conditions are used.

7. A person of ordinary skill in 1994 would not be able to determine the appropriate calibration standards to use to measure the AMW of copolymer-1 to allow for a meaningful comparison of a copolymer-1 sample to the '808 patent claims.

8. Several types of SEC calibration standards could have been known to a person of ordinary skill in 1994. A person of ordinary skill in the art in 1994 would understand that SEC calibration standards should ideally meet at least two important criteria:

(1) The SEC calibration standards and the sample of the same molecular weight must have the same hydrodynamic volume, and

(2) For monodisperse standards, each standard should have a known molecular weight; for polydisperse standards, each standard should have a known average molecular weight.

9. To my knowledge, in 1994, commercially-available SEC calibration standards were available that met criterion 2 and further experimentation would have had to be done to determine if they met criterion 1. These standards included, for example, globular protein standards such as those offered by Pharmacia (the manufacturer of Superose 12 columns in 1994) (Exhibit 2). The benefit of using these protein-based SEC calibration standards is that accurate molecular weights were known for each standard, because the standards typically have monodisperse molecular weights. In 1994, it would have been reasonable for a person of ordinary skill to try these standards first because (1) SEC analysis then could be performed in a reasonable amount of time using the readily available commercial

standards and (2) the choice of these well-defined standards with exactly known molecular weights would eliminate a significant source of ambiguity in choosing the methods for determining the average molecular weights of alternative polydisperse standards. If unknown and uncharacterized polydisperse polymer mixtures were used as standards, potentially significant errors would be introduced as discussed further below.

A. Self-standards produce different molecular weight results depending on how they are developed.

10. As discussed in Dr. Dubin's declaration (Dubin Declaration ¶27), another labor-intensive SEC calibration option in 1994, would have been to use batches of copolymer-1 as "self-standards." Each standard would consist of a polydisperse copolymer-1 mixture having a predetermined "average molecular weight." The benefit of these standards is that they may be more likely to meet "criterion 1" of paragraph 7, however, the average molecular weight would not be known with certainty.

11. A person of ordinary skill in 1994 would know that self-standards for SEC would give different molecular weight results depending on how they were developed. And the patents-in-suit and their corresponding prosecution histories say nothing about how to develop self standards to calibrate an SEC column.

12. A person of ordinary skill would have to estimate the average molecular weight of these standards using an independent absolute method. Several methods, such as ultracentrifugation, light

scattering, and intrinsic viscosity, were available in 1994 and could be used to independently estimate the average molecular weight of the copolymer-1 standards. Although each of these methods is described as an "absolute method," for the same polydisperse sample such as copolymer-1, each method typically will report very different average molecular weight values, with differences that can range up to 25% or more.

13. TEVA's own documents illustrate this point. For example, TEV001116167 (Exhibit 3) (excerpted below) shows the average molecular weights experimentally obtained by each of these absolute methods (*i.e.*, ultracentrifugation, light scattering and intrinsic viscosity) for the copolymer-1 standards used by TEVA in the 1994-95 timeframe. As can be seen from TEV001116167, depending on which absolute method was used, the results often varied by up to 20-30%.

Table 1

Average molecular weight of copolymer-1 markers obtained by ultracentrifugation, viscosimetry and SMALLS.

Marker	MW ultracentrifuge	MW viscosimetry	MW-SMALLS
01795	6000	7800	7400
BD-420	6200	8280	5200
BD-1710	6800	8380	5100
50695	7200	7800	8700
01695	7400	8580	8400
02095	7800	8800	5800
01496	8100	7800	7800
50595	8100	9300	7800
00895	8800	8780	9300
01195	9200	10000	10100
BD-422	13800	12400	15800
BD-403	13400	12480	14300
BD-516	16200	18400	17200
BD-402	26100	26200	22200
BD 114	33500	34000	31300

Excerpt form TEV001116167

14. The variance based on the absolute method chosen is further illustrated in the table below, which illustrates the differences in the molecular weight determinations described in TEV001116167.

Table 1 of Exhibit 1 to the 1st Declaration of Chang Ryu.

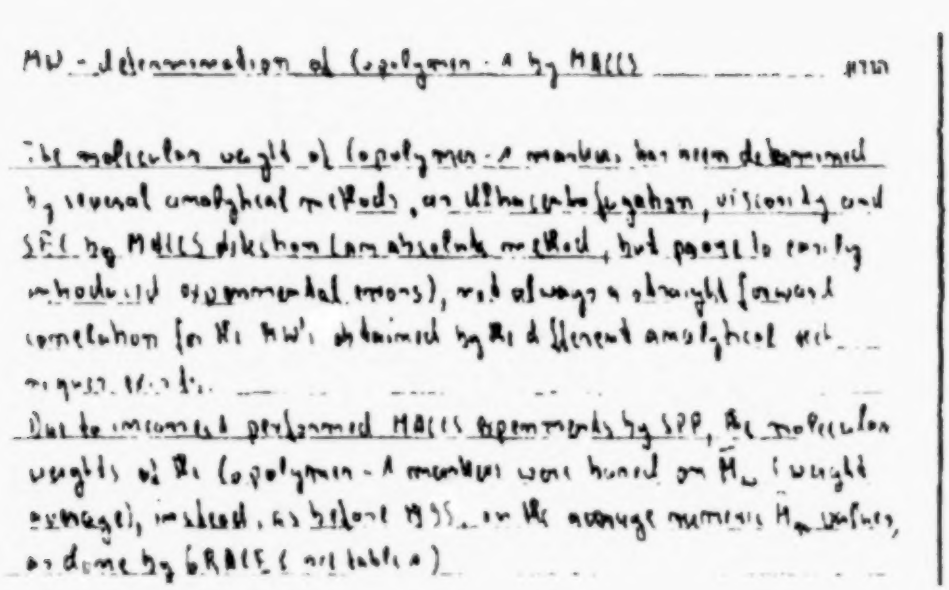
Marker	MW Ultracentrifuge	MW Viscometry	MW MALLS	Min Mw among 1	Max Mw among 3	Max Mn	Max Mw/Mn Ave of 3 MW's
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
BD-[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
BD-[illegible]	6800	6300	5100	5100	6800	1700	2.8
50695	7200	7900	8700	7200	8700	1500	1.8
01695	7400	8500	8400	7400	8500	1100	1.3
[illegible]	[illegible]	[illegible]	5800	5800	7900	2100	[illegible]
01495	8100	7800	7800	7800	8100	[illegible]	5.4
50595	[illegible]	9300	7900	7900	9300	1400	1.8
01855	8600	8700	9300	8600	9300	700	7.9
01195	9200	10000	10100	9200	10100	900	9.2
BD-422	13800	12400	15800	12400	15800	3400	24.1
BD-403	15500	12400	14900	12400	15500	3100	22.0
BD-515	16200	16400	17200	16200	17200	1000	6.6
BD-402	25100	25200	22200	22200	25200	3000	12.4
BD-114	33500	34000	31300	31300	34000	2700	8.2

15. Further, unless the calibration standard is monodisperse, for SEC characterization of copolymer-1, the person of ordinary skill in the art in 1994 would be confused as to which average molecular weight (*e.g.*, Mz, Mn, Mw) should be used to generate the calibration curve. Each of these methods is likely to give different average molecular weight values for a polydisperse standard. Ultracentrifugation reports either Mw or Mz (First Ryu Declaration ¶39), intrinsic viscosity measurements report Mv, and light scattering experiments measure Mw for a polydisperse polymer.

16. Thus, there exists a great source of ambiguity in estimating average molecular weights from SEC using self-standards, because the experimental

estimation depends on the choice of the type of average molecular weight used for the polydisperse standards in calibrating the SEC column. For example, when the weight average molecular weights of the polydisperse standards are used for the SEC calibration, different SEC results will be obtained than if the SEC calibration was based on the number average molecular weight of the same standards, or some other value such as Mz or Mv for the standards.

17. In fact, in the mid-1990s, Teva had two different vendors who performed SEC-MALLS analyses on samples of copolymer-1 in order for Teva to determine the average molecular weight of its copolymer-1 samples used as polydisperse self-standards for SEC. See TEV001013038 (Exhibit 4) (excerpted below). The vendor who was performing SEC-MALLS before 1995 (GRACE) reported to TEVA number average molecular weights (Mn) and the vendor who performed SEC-MALLS after 1995 (SPP) reported to TEVA weight average molecular weights (Mw). Further, as noted in the Teva document, the use of MALLS to determine the absolute AMW was "prone to easily introduced experimental errors."



MW - determination of Copolymer-1 by MALLS

The molecular weight of Copolymer-1 markers has been determined by several analytical methods, an ultracentrifugation, viscosity and SEC by MALLS detection (an absolute method, but prone to easily introduced experimental errors), not always a straight forward correlation for the MW's obtained by the different analytical techniques exists.

Due to incorrect performed MALLS experiments by SPP, the molecular weights of the Copolymer-1 markers were based on $\bar{M}_w$ (weight average), instead, as before 1995, on the average numeric $\bar{M}_n$ values, as done by GRACE (see table 1)

Excerpt from TEV001013038

18. For highly polydisperse standards such as copolymer-1 standards, the differences between the Mw and Mn can be very large. The polydispersity index (PDI), which is defined as Mw/Mn, is commonly reported in the scientific literature as a measure to represent the broadness in the molecular weight distribution of polydisperse polymers. Teva's own document (*see* TEV000990110 (Exhibit 5) (excerpted below)) shows that the differences between Mn and Mw determined by SEC-MALLS for batches of copolymer-1 routinely ranged from 35-45% (based on the PDI calculations). Therefore, the values of the calibration curve would be different by 35-45%, depending on whether the values of Mn or Mw of the copolymer-1 standard would be used for the SEC calibration. In other words, the observed average molecular weights obtained from the SEC calibration curve would differ by 35-45%, depending on which type of average molecular weight (*i.e.*, Mn or Mw) was used to calibrate the column.

Table I Molecular Weight Averages of COP-1 (g/mol)			
	Mn	Mw	Mz
R186-1	23,200 22,000 25,600	38,800 34,900 36,700	49,800 48,500 53,200
R186-3	7,300 8,200 9,200	11,000 11,500 13,200	13,800 16,700 15,100
R187	36,200 36,800 42,800	53,600 60,200 56,500	79,600 74,700 81,000
R189	6,600 6,700 5,700	9,800 9,900 9,500	13,900 13,100 12,100
R196-1	15,800 14,400 14,700	21,700 23,600 24,500	26,000 25,800 32,700
R196-2	13,900 10,200 11,100	15,200 20,300 16,500	24,700 29,300 20,500
DL747-2	6,200 6,300 6,100	8,400 8,200 8,600	11,800 12,500 11,300
DL747-3	5,700 4,200 4,000	6,900 5,400 6,500	8,800 7,800 8,000

Excerpt from TEV000990110

19. Even under the incorrect assumption that the term "average molecular weight" in the patents-in-suit must mean the peak molecular weight, there still exists a significant source of experimental error in obtaining the different kinds of average molecular weights via SEC. This is because of the mismatch between the peak molecular weight and the average molecular weights obtained from the absolute techniques, such as ultracentrifugation, light scattering, and intrinsic viscosity. Depending on which type of average molecular weight is used to

calibrate the SEC column, the average molecular weight values will be significantly affected.

20. The patents-in-suit and prosecution histories say nothing about which standards a person of ordinary skill should use, much less that one should make and use unknown copolymer-1 as "self-standards." There likewise is no mention of which absolute method and which average molecular weight should be used to develop copolymer-1 standards as polydisperse SEC calibration standards. Without this information, a person of ordinary skill would be confused in developing their own copolymer-1 SEC calibration standards and expect that they would not give similar results as reported in the '808 patent.

B. Universal SEC calibration suffers from uncertainties just like self-calibration.

21. In 1994, a person of ordinary skill in the art attempting to perform universal calibration to measure the molecular weight of copolymer-1 by SEC would run into the same problems encountered with developing a self-standards calibration method. Namely, which absolute molecular weight method should be used to develop the universal SEC calibration method. In order to use universal calibration, a person of ordinary skill would have to experimentally obtain the values of the "K" and "a" constants in the Mark-Houwink equation for both the standards and samples. To accomplish this, a person of ordinary skill would measure the intrinsic viscosity of a number of different sized copolymer-1 batches or fractions by using glass capillary viscometers at the same solution conditions that will

be used in the SEC analysis. Then, a person of ordinary skill would need to also measure the average molecular weights of the same copolymer-1 samples used in the intrinsic viscosity measurements using one of the absolute molecular weight techniques (*i.e.*, ultracentrifugation, light scattering, etc.). From this data, a person of ordinary skill could calculate "K" and "a" for copolymer-1 used for the SEC analysis. Of course, as discussed above, depending on which absolute molecular weight method is chosen (ultracentrifugation, light scattering, etc.), the "K" and "a" values of polydisperse copolymer-1 sample will vary greatly. Therefore, the uncertainty of the average molecular weights from the universal SEC calibration will be greatly influenced by the polydispersity of copolymer-1 and the potential errors of absolute molecular weight methods.

C. Intra- and Inter-laboratory studies demonstrate the importance of standards and conditions.

22. In 1994, it was well known to persons of ordinary skill that when SEC conditions are not agreed upon between two laboratories, significantly different average molecular weight values could be expected for the SEC analysis of polydisperse polymers, such as copolymer-1, even when analyzing the exact same sample.

23. A series of studies called "Round Robin" studies were conducted between 1987 and 1994 to quantitatively estimate this laboratory-to-laboratory variation observed when obtaining average molecular weights using SEC. Several of these

studies, summarized in Exhibits 6 and 7, were conducted using well-known polydisperse synthetic polymer samples, such as polystyrene.

24. In 1994, copolymer-1 was not as well-characterized and as widely-available as the polymer samples used in the Round Robin studies. Thus, although these studies provide important reference points with respect to how much variation two laboratories may expect for well-characterized polydisperse polymer samples, these results should be viewed as best case scenarios with respect to the analysis of copolymer-1. An even greater degree of variation would be expected if two different laboratories analyzed the same copolymer-1 sample in 1994 and did not agree on the conditions and calibration methods prior to performing the analysis.

25. Several of the Round-Robin studies indicated, when the SEC conditions are not agreed upon and the analysis is conducted at different laboratories (also known as the "reproducibility") the variation in average molecular weight measurements increases significantly. For number average molecular weight (Mn), the laboratory-to-laboratory reproducibility was approximately 16-18%. Exhibit 7 at p. 16. For weight average molecular weight (Mw), the reproducibility was approximately 7-10%. Exhibit 7 at p. 16.

26. Because the '808 patent does not disclose the specific calibration standards and conditions, a person of ordinary skill in the art in 1994 would expect uncertainty levels similar to the reproducibility results discussed above, at best. It is likely the reproducibility of SEC measurements of

copolymer-1 would be at least in the range of 7-18%, if not significantly higher. Operating under this level of uncertainty, a person of ordinary skill in the art in 1994 would find it difficult and uncertain to know whether their copolymer-1 sample had an average molecular weight of 9 or 10 kDa.

4. Superose 12 columns could yield inaccurate and widely varying results under different conditions.

27. A person of ordinary skill in 1994 would know that estimating the molecular weight of proteins using Superose 12 may give inaccurate and widely varying results under different conditions.

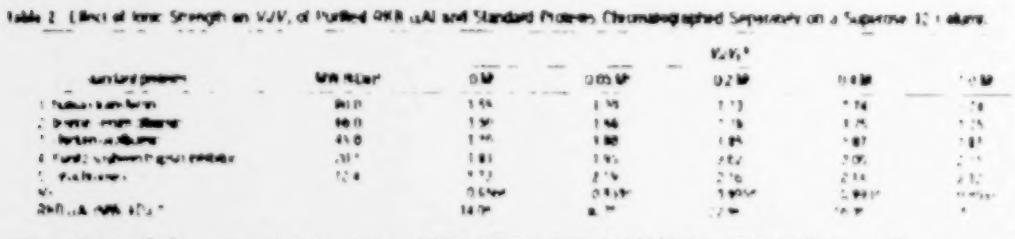
28. In paragraph 23 of his second declaration (Second Grant Declaration ¶23), Dr. Grant attempts to "illustrate how persons of ordinary skill in the art could employ varying SEC standards and conditions to measure the molecular weight of a particular sample and reach consistently accurate results" by describing the scientific literature of two well-characterized and widely-available proteins: glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and L-lactate dehydrogenase (LDH).

29. First, these examples relate to single proteins rather than polydisperse copolymer mixtures. That is, the two protein examples mentioned by Dr. Grant describe a single polypeptide without any polydispersity in molecular weight, whereas copolymer-1 contains millions upon millions of different polypeptides.

30. Even under this simple circumstance, Dr. Grant's analysis is misleading as he did not consider

scientific literature illustrating how conditions can dramatically affect both the accuracy and precision of a molecular weight analysis of single proteins. For example, consider the 2004 article by Lee and Whitaker entitled "Are Molecular Weights of Proteins Determined by Superose 12 Column Chromatography Correct?" Exhibit 8. This article reports on the measurement of the molecular weight of a well-characterized and widely-available protein red kidney bean a-amylase inhibitor (RKB αAI) – using the Superose 12 column described in example 1 of the patents-in-suit. The authors found that the molecular weight estimate of this protein changed depending on the ionic strength of the buffer used during the Superose 12 separation. Furthermore, the authors were able to conclude that none of the estimates determined by the SEC under different ionic strength conditions were accurate.

31. The pertinent results from this study were summarized in Table 2 of the Lee and Whitaker article. The results from Table 2 are adapted and shown in the table below:



Effect of Ionic Strength on Molecular Weight Estimates using Superose 12
(adapted from Table 2 of Exhibit 8)

32. This Lee and Whitaker article demonstrates two important points: First, as indicated in footnote *e* in the table above, the standards and the sample (in this case RKB αAI) were run under identical conditions. However, conducting the experiment in this manner did not prevent significantly different molecular weight results at each ionic strength tested. The molecular weight results ranged from 14.0 to 30.7 kDa (*see* row 7 in the table above). Second, a person of ordinary skill performing this kind of SEC analysis using Superose 12 column for the first time would not know which of these values corresponded to the accurate[24] molecular weight. Indeed, only after the comparison with other independent methods of determining the molecular weight of RKB αAI, the authors were able to convincingly conclude that none of the molecular weight estimates from their Superose 12 analysis were accurate. This illustrates the point that the accuracy of molecular weights based on the SEC should only be concluded after employing two or more molecular weight methods preferably based on different underlying principles.

33. A person of ordinary skill in the art in 1994 would have appreciated that while in some instances SEC could be used to determine accurate molecular weight results of single proteins (Second Grant Declaration ¶23), there were also several instances

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[24] By accurate I mean closely approximating the true molecular weight value.

where the technique could report inaccurate molecular weight results for single proteins (Exhibit 9).

34. If SEC, in certain circumstances, reports inaccurate molecular weight results for single proteins, it would be very likely to report inaccurate results for polydisperse samples containing millions upon millions of different polypeptides, such as copolymer-1. Therefore, a person of ordinary skill in the art in 1994 would know that it is difficult to obtain the accurate average molecular weights of copolymer-1 samples that are polydisperse and contain mixtures of different polypeptide molecules.

35. The patents-in-suit do not mention any molecular weight analysis of copolymer-1 aside from the SEC analysis described in Example 1. Not having any independent confirmation of the SEC results in Example 1, a person of ordinary skill in the art in 1994 would have significant reason to doubt the accuracy of the molecular weight values reported in this Example.

I declare under penalty of perjury that the factual statements contained herein are known by me or believed by me to be correct.

Dated: July 09, 2010

_____

Chang Ryu

[EXHIBITS 1-9 OMITTED]

No. 13-854

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

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June 13, 2014

PETITION FOR A WRIT OF CERTIORARI FILED JANUARY 16, 2014
CERTIORARI GRANTED MARCH 31, 2014

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC., and YEDA RESEARCH AND DEVELOPMENT CO. LTD.,

Plaintiffs,

v.

SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC.,

Defendants.

08 Civ. 7611 (BSJ) (AJP)

Memorandum and Order

BARBARA S. JONES
UNITED STATES DISTRICT JUDGE

Defendants Sandoz, Inc., Sandoz International GmbH, Novartis AG, and Momenta Pharmaceuticals, Inc. moved for summary judgment on the basis that the patents at issue are invalid because their claims are indefinite under 35 U.S.C. § 112.[25] As part of their opposition to Defendants' motion for summary judgment, Plaintiffs Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. submitted expert declarations from Dr. Gregory Grant and Dr. Paul Dubin. Defendants subsequently moved to strike both declarations. For the reasons provided below, Defendants' motions for summary-judgment and to strike Plaintiffs' expert declarations are DENIED.

I. Defendants' Motion to Strike the Expert Declarations

In Daubert v. Merrell Dow Pharmaceuticals, Inc., the Supreme Court explained that expert testimony is admissible where it "rests on a reliable foundation and is relevant to the task at hand." 509 U.S. 579, 597 (1993). Here, the challenged declarations are both reliable and relevant.

A. Reliability

Defendants' primary argument regarding reliability is that the declarations should be excluded because neither Dr. Grant nor Dr. Dubin has

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[25] On August 26, 2010, Plaintiffs voluntarily dismissed, without prejudice, their claims against Sandoz International GmbH and Novartis AG. Accordingly, all references to "Defendants" hereinafter are only to Sandoz, Inc. and Momenta Pharmaceuticals, Inc.

knowledge regarding "what Teva actually did." First, according to Defendants, Dr. Grant undermined his own opinion by criticizing the approach that Teva used to characterize its own copolymer-1 standards. Second, Defendants claim that Dr. Grant's opinion hinges on "speculative rationalization," as opposed to objective analysis, because he did not verify his measurements against Teva's actual data for copolymer-1. Third, Dr. Dubin's opinion, according to Defendants, contradicts the facts of Teva's molecular weight analysis because Teva did not use "the same mobile phase" for the chromatographic separation and molecular weight analysis of copolymer-1. Defendants contend that Dr. Dubin's opinion also contradicts Teva's molecular weight analysis because universal calibration would not have been routine for copolymer-1 because copolymer-1 is "highly charged" and universal calibration works for polymers of that nature only occasionally. Lastly, Defendants claim that the opinion of both experts, that "it would have been routine" to analyze copolymer-1 using either self-standards or universal calibration, is unreliable because they contradict Teva's own experiences with copolymer-1. According to Defendants, use of copolymer-1 standards was not routine at the time of filing and size exclusion chromatography ("SEC") analysis of copolymer-1 would not have been routine due to complications caused by electrostatic effects.

The fact that Dr. Grant and Dr. Dubin do not have knowledge of "what Teva actually did"—either personally or by reviewing Teva's internal documents—does not warrant excluding their declarations. In Daubert, the Supreme Court

explained that expert witnesses are permitted "wide latitude to offer opinions, including those that are not based on firsthand knowledge or observation." 509 U.S. at 592 (citations omitted). The "relaxation of the usual requirement of firsthand knowledge is premised," the Court added, "on an assumption that the expert's opinion will have a reliable basis in the knowledge and experience of his discipline." Id. (citation omitted).

Daubert is particularly apt here because the only information Dr. Grant and Dr. Dubin needed regarding "what Teva actually did," in order to render an opinion on Defendants' indefiniteness claim, is the information disclosed in the patents themselves and in the prosecution history. See, e.g., Kinetic Concepts, Inc. v. Blue Sky Med. Grp., Inc., 554 F.3d 1010, 1022 (Fed. Cir. 2009) ("The definiteness analysis requires a determination of 'whether one skilled in the art would understand the bounds of the claim when read in light of the specification.'") (citations omitted). It is beyond dispute that a person of ordinary skill in the art, such as Dr. Grant and Dr. Dubin—a point unchallenged by Defendants—would not have had access to Teva's internal documents. In fact, because neither expert refers back to "what Teva actually did," both opinions carry a greater degree of objectivity than they otherwise would if they did refer to "what Teva actually did."

To the extent that Defendants argue that the opinions of Dr. Grant and Dr. Dubin are unreliable because they are inconsistent with their deposition testimony, previous declarations, or previous writings, these critiques speak, at most, to

credibility. As a court in this district recently explained, "[q]uestions of credibility generally do not render an expert's testimony inadmissible." In re Pfizer Inc. Sec. Litig., No. 04 Civ. 9866(LTS){JLC), 05 md 1688(LTS), 2010 WL 1047618, at *2 (S.D.N.Y. Mar. 29, 2010) (citing Daubert, 509 U.S. at 596). Issues of credibility, such as those alleged here, are best explored through "[v]igorous cross-examination." See Daubert, 509 U.S. at 596.

In addition to their reliability arguments based on lack of knowledge of "what Teva actually did," Defendants also argue that Dr. Grant's opinion that Figure 1 teaches peak molecular weight is unreliable (1) because he allegedly did not consider the possibility that Figure 1 refers to weight-average molecular weight (Mw) and (2) because the methodology of his analysis has not been tested.

Defendants' first claim is demonstrably false. In Dr. Grant's first declaration, dated October 6, 2009 and expressly incorporated into his declaration in opposition to Defendants' motion for summary judgment, Dr. Grant explicitly explained why a person of ordinary skill in the art would not have interpreted Figure 1 to refer to weight-average molecular weight (Mw) (Grant Decl. ¶¶ 63-64, Oct. 6, 2009.) Any claim that Dr. Grant impeached himself is, again, best explored through "[v]igorous cross-examination." See Daubert, 509 U.S. at 596.

Defendants' other arguments—that Dr. Grant's methodology is flawed because it has not been subjected to peer-review, because his technique has

not been generally accepted by the relevant scientific community, and because he has not articulated a meaningful error rate—are also unpersuasive. After a careful review of Dr. Grant's summary judgment opposition declaration, his first declaration (dated October 6, 2009), his second supplemental declaration (dated November 4, 2009), his third supplemental declaration (dated November 17, 2009), all of which discuss Dr. Grant's interpretation of Figure 1 in great detail, even assuming there is an issue regarding Dr. Grant's methodology, exclusion is not warranted. It also bears worth noting that Defendants did not offer the opinion of a single expert discrediting or casting doubt on Dr. Grant's methodology or his interpretation of Figure 1.

B. Relevancy

With respect to Daubert's relevancy requirement, Defendants argue that the declarations are inadmissible because Dr. Grant and Dr. Dubin both address the wrong question. According to Defendants, both experts testify "that skilled artisans would know what standards or conditions to use to accurately determine their own molecular weight," while ducking "the proper question of indefiniteness"—namely, whether a skilled artisan "could meaningfully compare the molecular weight of his or her copolymer-1 to the molecular weight values as determined by Teva and recited in its claims." This requires, Defendants claim, "using the same measurement standards and conditions as Teva."

In order to properly consider the relevancy of the declarations, it is imperative to take into account Defendants' indefiniteness arguments. In their motion for summary judgment, Defendants argue, first, that the patents at issue are indefinite because Teva did not expressly define average molecular weight. Defendants argue, second, that the patents are indefinite because Teva failed to disclose the SEC standards and calibration conditions necessary to determine if an accused product's molecular weight matches Teva's claimed molecular weights.

With respect to Defendants' first argument, in his declaration, Dr. Grant explains why a person of ordinary skill in the art would have understood that the average molecular weight reported in the patents' specifications refers to peak average molecular weight. Dr. Grant also provides a detailed description of why a person of ordinary skill in the art would not have understood average molecular weight to refer to number average molecular weight (Mn), weight average molecular weight (Mw), z average molecular weight (Mz), or viscosity average molecular weight (Mv)—the other possible meanings identified by Defendants. Thus, Dr. Grant's declaration is clearly relevant to Defendants' first indefiniteness argument.

With respect to Defendants' second argument, Dr. Grant and Dr. Dubin both opine that, since 1994, a person of ordinary skill would not have needed to know or use the same measurement standards and conditions as Teva in order to understand what Teva claimed. Since 1994, according to Dr. Grant and Dr. Dubin, a person of

ordinary skill would be independently capable of selecting appropriate calibration standards and SEC conditions to determine if an accused product's molecular weight matches Teva's claimed molecular weight values. Because both declarations address the proper definiteness analysis—namely, whether the meaning of the claim is "discernible," see, e.g., Exxon Research and Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001) (citations omitted)—they are relevant to Defendants' second indefiniteness argument.

To the extent Defendants made arguments not explicitly addressed in this Memorandum and Order, the Court has considered these arguments, and finds they do not warrant excluding Plaintiffs' experts' declarations.

II. Defendants' Motion for Summary Judgment

As the moving party, Defendants bear the burden of demonstrating "the absence of a genuine issue of material fact" that the patents at issue are indefinite (1) because Teva did not expressly define average molecular weight and (2) because Teva failed to disclose the SEC standards and calibration conditions necessary to determine if an accused product's molecular weight matches Teva's claimed molecular weights. See, e.g., Celotex Corp. v. Catrett, 477 U.S. 317, 323 (1986).

With respect to Defendants' first argument, in his declaration, Dr. Grant explained that a person of ordinary skill in the art would have understood that the average molecular weight reported in the patents' specifications refers to peak average. In

addition to Dr. Grant's declaration, in its opposition, Teva explained that the term "average molecular weight" first appeared in the "539 patent. When the patent examiner rejected claims directed to that term, on the precise indefiniteness grounds that Defendants assert here, Teva explained that a person of ordinary skill in the art would understand, upon reviewing the specification, that ""average molecular weight' refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1." (Doyle Decl. Ex. 11 (v 539 Patent, Dec. 1, 2004 Amendment at 10).) The examiner accepted that explanation and issued a Notice of Allowability. See, e.g., Mas-Hamilton Grp. v. LaGard, Inc., 21 F. Supp. 2d 700, 717 (E.D. Ky. 1997) ("There is a (heavy presumption against [Defendants] in arguing that the patens and claims do not comply with 35 U.S.C. § 112 where the Examiner reviewed the adequacy of the descriptions and found the patent descriptions to be definite and allowed the patents thereafter.'") (citations omitted).

Defendants claim that statements Teva made while prosecuting the other patents are inconsistent with the reference to peak average. Even assuming Defendants are correct, which does not appear to be the case in light of Teva's explanation regarding why none of the other statements identified by Defendants conflict or undermine the reference to peak average, Teva has provided more than ample evidence to demonstrate that there is a genuine issue of material fact regarding whether the patents adequately defined average molecular weight. See, e.g., Santos v. Murdock, 243 F.3d 681, 683 (2d Cir.

2001) ("Once a party moving for summary judgment has made the requisite showing that there is no factual dispute, the nonmoving party bears the burden of presenting evidence to show that there is, indeed, a genuine issue for trial.") (citing Celotex Corp., 477 U.S. at 323-24).

With respect to its second indefiniteness argument, Defendants concede that the *161 patent specification expressly identifies SEC as a method for determining the molecular weight distribution of copolymer-1. Despite identifying this particular method, Defendants argue that the patent claims are invalid because Teva omitted "essential" information regarding how to set the testing standards and conditions to achieve Teva's claimed molecular weights.

Teva's experts, Dr. Grant and Dr. Dubin, rebut Defendants' argument by explaining that, since 1994, a person skilled in the art would not need to know the exact SEC standards and conditions Teva used. Since 1994, according to Dr. Grant and Dr. Dubin, a person of ordinary skill in the art would be capable of independently selecting appropriate SEC standards and conditions to determine if an accused product's molecular weight matches Teva's claimed molecular weights.

Defendants present no expert testimony directly challenging the opinions of Plaintiffs' experts. Instead, Defendants point to excerpts from Dr. Grant's deposition testimony and to other internal Teva documents in an effort to show that it is "impossible" to know whether an accused product's molecular weight matches Teva's claimed molecular

weights without using the same SEC standards and conditions as Teva. Defendants essentially offer nothing more than attorney argument. In light of Plaintiffs' experts' declarations, Defendants fail to demonstrate they are entitled to summary judgment on their second indefiniteness argument. See Invitrogen Corp. v. Clontech Labs., Inc., 429 F.3d 1052, 1068 (Fed. Cir. 2005) ("Unsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony."), see also Glaverbel Societe Anonyme v. Morthlake Mktg. & Supply, Inc., 4 5 F.3d 1550, 1562 (Fed. Cir. 1995) ("There must be sufficient substance, other than attorney argument, to show that the issue requires trial.") (citations omitted).

Although Defendants' theories of indefiniteness do not warrant summary judgment, in light of the emphasis Defendants place on it, it is important to explain why Defendants' reliance on Honeywell International, Inc. v. International Trade Commission, 341 F.3d 1332 (Fed. Cir. 2003), is misplaced. In Honeywell, the patent holder taught one example for measuring the "melting point elevation" ("MPE") of polymer yarn for automobile tires. Id. at 1335-36. It failed, however, to disclose any method for preparing the yarn for measurement. Id. at 1336. As of the earliest priority date of the Honeywell patent, only "[t]hree sample preparation methods were published in the art." Id. A fourth method existed, but was unpublished and documented only in the patent holder's proprietary files. Id. The Federal Circuit found that "knowing the proper sample preparation

method is necessary to practice the invention" because the calculated MPE could "vary greatly" based on which method was used. Id. at 1336, 1340. Because "the claims, the written description, and the prosecution history" gave no "guidance as to what one of ordinary skill in the art would interpret the claim to require," the Federal Circuit found the claims "insolubly ambiguous." Id. at 1340.

Here, by contrast, Teva specifically identified SEC as a method for determining the molecular weight distribution of copolymer-1. In response to the patent examiner's initial rejection of the term "average molecular weight" during the prosecution of the '539 patent—specifically on the basis of Honeywell—Teva also explained that upon reviewing the specification, a person of ordinary skill in the art would understand that ""average molecular weight' refers to" peak average molecular weight. (Doyle Decl. Ex. 11 ("539 Patent, Dec. 1, 2004 Amendment at 10).) Because intrinsic evidence directly instructs how a person of ordinary skill in the art should interpret the term "average molecular weight," Honeywell is not controlling.

To the extent Defendants made arguments not explicitly addressed in this Memorandum and Order, the Court has considered these arguments, and finds they do not warrant summary judgment.

CONCLUSION

For the reasons provided above, Defendants' motions for summary judgment (Dkt. 121) and to strike the expert declarations of Dr. Grant and Dr. Dubin (Dkt. 144) are DENIED.

SO ORDERED:

BARBARA S. JONES
UNITED STATES DISTRICT JUDGE

Dated: New York, New York
September 7, 2010

[Excerpt from the September 7, 2011 Trial Testimony of Gregory A. Grant, Ph.D.]

* * *

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* * *

PTX99, PTX523, PTX538, PTX591, 565, 605, 616, 617, 623, 626, 627 and 644 and plaintiffs would move for the admission of all of those into evidence.

THE COURT: I don't believe there were any objection as we went through these. Unless I hear one now, they're admitted. Yes, Mr. Doyle?

MR. DOYLE: Your Honor, just assuming that these are the published articles upon which this expert has relied.

THE COURT: That's what I believe they are.

MR. DOYLE: Thank you.

(Plaintiff's Exhibits PTX99, PTX523, PTX538, PTX591, 565, 605, 616, 617, 623, 626, 627 and 644 received in evidence)

THE COURT: Any redirect?

MR. BENNETT: No, your Honor.

THE COURT: Thank you, Dr. Lisak. You're excused. (Witness excused)

THE COURT: Who is your next witness?

MR. JAMES: Plaintiffs call Dr. Gregory Grant.

THE COURT: All right, Dr. Grant.

MR. ACKER: Your Honor, I want to introduce myself, I'm Eric Acker and I'll be cross-examining Dr. Grant.

THE COURT: All right. I'm glad you did.

GREGORY GRANT, called as a witness by the Plaintiff, having been duly sworn, testified as follows:

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DIRECT EXAMINATION BY DR. JAMES:

Q. Good afternoon, Dr. Grant.

A. Good afternoon.

Q. Could you tell us where you reside?

A. I live in St. Louis, Missouri.

Q. Are you employed?

A. Yes, I am.

Q. By whom are you employed?

A. By the Washington University School of Medicine.

Q. What is your position there?

A. I am a professor of biochemistry of medicine and of developmental biology.

Q. Do you hold any other positions at Washington University, Dr. Grant?

A. Yes, I'm also the director of the protein and nucleic acid chemistry laboratories of Washington University.

Q. What is the protein and nucleic acid chemistry laboratory?

A. It's a laboratory that does studies for other scientists both inside and outside of the university.

Q. What types of researchers seek the assistance of your laboratory, Dr. Grant?

A. We have many different types of researchers. Some are just basic researchers looking at biochemistry questions. Some are researchers looking into investigation into diseases and some [179] are also physicians who actually treat patients.

Q. And what types of assistance do you offer them?

A. We do tests for them. Over the years, we've done many different types of tests. They include things like determining the molecular weights of proteins, determining the amino acid compositions of polypeptides and proteins, determining nucleic acid sequence of polypeptides. I've also synthesized polypeptides in the laboratory and right now we have a very large effort in DNA sequencing.

Q. How long have you been the professor of the protein and nucleic acid chemistry laboratory?

A. Next year it will be three years.

Q. Could you briefly summarize your educational background for the Court?

A. Yes. I went to Iowa State University, got my bachelors degree in biochemistry. From there I moved on to the University of Wisconsin Madison where I achieved my PhD in biochemistry. Then I

moved on to St. Louis as a post doctoral fellow studying protein chemistry.

Q. What year did you receive your PhD?

A. 1975.

Q. What was the topic of your thesis?

A. It dealt with the study of proteins in blood clotting.

Q. Dr. Grant, you said you have a PhD in biochemistry? What is biochemistry?

[180]

A. Biochemistry is basically the study of chemistry that is found in the molecules of living organisms.

Q. Can you give us some examples of those kinds of molecules?

A. Yes. Examples are proteins, polypeptides, would include enzymes, those are the basic things that I study.

Q. What was the subject of your post doctoral research?

A. My post doctoral research studies characteristics or properties of various different proteins and enzymes.

Q. There's a lot of talk in this case about proteins and polypeptides. Could you tell us what the difference is between those two things?

A. Proteins are polypeptides.

Q. Could you explain that a little further? Why is that?

A. Because they're both made up of amino acids. Not all polypeptides are considered proteins, but all proteins are polypeptides.

Q. Why is it called a polypeptide?

A. It's called that because it's made up of amino acids that are joined together by bonds and poly simply means -- the bond is called a peptide bond. Poly simply means there are many of them.

Q. Is copolymer-1 made up of polypeptides?

A. Yes, it is.

Q. Now, as part of your post doctoral research, Dr. Grant, what in particular did you study about proteins?

[181]

A. I studied many aspects of proteins, but it included determining the amino acid composition, the sequence of proteins, and we also do quite a bit of work with determining the molecular weight using size exclusion chromatography a lot during that time.

Q. Since you completed your post doctoral research, Dr. Grant, what positions have you held?

A. After my post doc, I stayed on at Washington University as an assistant professor and then over the years I rose through the ranks through associate professor and then full professor.

Q. What year did you become a full professor?

A. 1995.

Q. Turn in -- let me get you some binders here, Dr. Grant, just one second.

MR. JAMES: For the record, your Honor, I've handed up two binders that have the under seal unredacted versions of the exhibits. The parties have worked together to try to come to some agreement on the confidentiality issues. I handed to Mr. Gomez a copy of the binder with public versions of the documents. If the documents ever become public we would ask that it would be those public redacted versions to be put in the public record.

MS. BLOODWORTH: Your Honor, if I may, this is Shannon Bloodworth for Mylan defendants. I believe our version of the documents are not in this binder, but we will be providing them [182] shortly.

THE COURT: What am I looking at?

MR. JAMES: You're looking at the unredacted version.

Q. Dr. Grant, could you turn in your binder to PTX760, please?

A. Okay.

Q. Can you identify that document, please?

A. Yes. It's a copy of my curriculum vitae.

Q. Is it reasonably accurate and up to date?

A. Yes, it is.

MR. JAMES: Your Honor, we would offer into evidence Plaintiff's Trial Exhibit 760.

MR. ACKER: No objection.

THE COURT: All right, admitted. Thank you Ms. Bloodworth.

(Plaintiff's Exhibit PTX 760 received in evidence)

Q. Dr. Grant, over the course of your career what has been the focus of your research?

A. The focus of my research has been almost exclusively on enzymes, proteins and polypeptides.

Q. What are enzymes?

A. Enzymes are proteins that carry out specific functions in the body. For instance, the proteins that help you digest your food are enzymes.

Q. And how many peer reviewed publications do you have?

A. I have over 120.

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Q. And how many of these publications address protein chemistry?

A. Nearly all of them.

Q. Have you edited any books, Dr. Grant?

A. Yes, I have. I've edited a book called "Synthetic Peptides: A Users Guide," and for several years I was editor on Techniques of Protein Chemistry.

Q. Your book on synthetic peptides, what is the subject matter of that book?

A. A peptide is the same thing as a polypeptide and the subject of that book is the design, the synthesis, the study and analytical examination of polypeptides.

Q. What is a synthetic polypeptide?

A. A synthetic polypeptide is the same as a polypeptide that's made by a scientist in the laboratory.

Q. Do synthetic polypeptides have any relevance to the case we're here to talk about today?

A. Yes, they do. Copolymer-1 is a mixture of synthetic polypeptides.

Q. Dr. Grant, have you been active in any professional organizations?

A. Yes. I've been active in several organizations. The one I would point out is the Association of Biomolecular Resource Facilities. It's an international organization of scientists who are interested in developing methods for things like [184] determining the molecular weights of polypeptides, their amino acid compositions, their sequences and so forth.

Q. Have you held any leadership roles in that society?

A. Yes. I've been active on several committees in that society and I served as president of that society in 1993 and 1994.

Q. Have you served on any editorial boards for any journals?

A. Yes. I have also served on several editorial boards. Again, the one I think that I would point out is the journal of biological chemistry, which is the preeminent journal of biochemistry in the world.

Q. How does one get to serve on an editorial board, Dr. Grant?

A. You're invited by the executive editor of the journal, based upon your knowledge and your expertise.

Q. Have you served on any advisory committees for any governmental agencies?

A. Yes. I've been on several advisory committees for the National Institutes of Health.

Q. Can you tell us what you do when you serve on these advisory committees?

A. These advisory committees are called study sections and what we do is we receive grant applications from other scientists throughout the country and we look at them and try to evaluate them for their scientific merit, their scientific rigor and their worthiness for funding.

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Q. What types of grant applications have you reviewed in the study sections that you participated in?

A. I reviewed the types of applications that meet my expertise, so almost all of them have dealt with some subject dealing with proteins or polypeptides or enzymes.

Q. Do you review grant applications having to do with the use of size exclusion chromatography?

A. Many of these applications will have that in them, yes.

Q. How many grants per year do you do when you're serving on a study section?

A. At the time I was doing it, I would say probably I review 40 or 50 grants a year.

Q. In addition to your duties at Washington University have you done any invited lectures?

A. Yes. I've done many invited lectures both in the United States and internationally.

Q. What do your lectures focus on?

A. Well, they can focus on various things, but mostly some of the lectures will be about my own research, while other of the lectures will be about the techniques that we use in the resource laboratory that I also direct.

Q. Have you taught any courses in your career?

A. Yes, I've taught courses to graduate students, they're graduate level courses. I mainly focus on proteins and polypeptides and I've taught large sections on how to study [186] them what the analytical techniques are and how to use them.

Q. What types of analytical techniques have you taught?

A. One that's relevant to this case of course is size exclusion chromatography.

Q. Could you tell us, what exactly is size exclusion chromatography?

A. Size exclusion chromatography is a method that allows you to separate proteins based upon their size, one from another, if they're all together in a mixture you can separate them so that they're not

together any more. But it's also a method that allows you to determine their molecular weight.

Q. You said it allows you to separate proteins. Does it allow you to separate polypeptides as well?

A. Yes. I'm using proteins and polypeptides sort of interchangeably, but polypeptides certainly.

Q. What is the relevance of size exclusion chromatography to this case?

A. The relevance is that patents in suit list size exclusion chromatography as the method to use to determine the molecular weight of copolymer-1.

Q. Dr. Grant, are there different areas of size exclusion chromatography based on the purpose for which you're using the technique?

A. Yes. They're basically two areas, I guess. One is called, the focus on fractionation, which is simply the process of [187] training to separate one molecule from another, but in addition to that, there's a distinct other area that is analytical in nature, which is determining the molecular weight of those proteins, which uses size exclusion chromatography.

Q. Do you have experience with the use of SEC as an analytical tool?

A. Yes, I do.

Q. Now, a minute ago you mentioned fractionation. Could you explain to the Court what that means?

A. Fractionation is taking a mixture of things and separating them so they're no longer in mixture.

In some instances you can actually purify them completely. The fractionation basically is trying to take a whole and divide it into fractions that contain different substances.

Q. Are there distinctions in SEC depending on the sample that you're analyzing?

A. Yes, there are. You can use SEC in an aqueous mode, by that I mean in water or a water-based solvent of some sort. SEC is also used with organic solvents. Which one you use really has a lot to do with the type of molecule that you're studying, and which one you use there are different interactions, so we say they're different ways the molecule will separate and different properties they will have in solution.

Q. Do you have experience with aqueous size exclusion [188] chromatography?

A. I have a lot of experience, yes.

Q. How long have you been doing aqueous size exclusion chromatography?

A. I've probably been doing that for 40 years or more.

Q. How many times would you say that you or someone under your supervision has performed aqueous size exclusion chromatography over the course of your career?

A. It would be hard to put a number on it, but certainly it's hundreds, might even be approaching thousands.

MR. JAMES: Your Honor, we would offer Dr. Grant as an expert in the characterization of

proteins and polypeptides using size exclusion chromatography.

THE COURT: Any objection or voir dire?

MR. ACKER: Not at this time, your Honor, no.

THE COURT: All right, then I accept Dr. Grant as an expert in that field.

Q. Dr. Grant, did you put together a set of slides to accompany your testimony today?

A. Yes, I did.

Q. Let's put up the first slide. And Dr. Grant, could you explain to the Court the subject matters that you're going to testify about today?

A. Yes. This slide is just an overview of that, of those subject matters and I've grouped them into two categories. The [189] first is, there's a background on the technology that's mentioned in the patents in suit and that is the copolymer-1 production itself and the use of size exclusion chromatography to analyze it, to determine its molecular weight. And then the second is the application of the claims to the defendants' ANDA products and I'm going to compare the ANDA products with the molecular weight claim terms that are in the patents.

Q. Thank you, Dr. Grant. Could you turn in your binder to Plaintiff's Trial Exhibit 1?

A. Okay.

Q. Do you recognize that to be a copy of the 808 patent?

A. Yes I do.

MR. JAMES: Your Honor, the patents in suit have been admitted in the July trial.

THE COURT: Yes, they're all in.

Q. Now, Dr. Grant, can you tell me the date that the application was first filed for the patents in suit?

A. That's May 24, 1994.

Q. And do you have an understanding of the level of skill in the art in this case?

A. Yes, I believe it to be high level.

Q. Let's look at the next slide. Dr. Grant, could you explain what's shown in this slide?

A. Yes. This is my definition of a person with skill in the art. They're a person that needs to have an advanced degree or [190] something very equivalent to that in a chemical or biological discipline and they need to have significant experience in the synthesis or characterization of polymers and certainly in the proteins or synthetic peptides. In addition to that, the person would have access to other scientists who have expertise in those areas.

Q. Dr. Grant, did you analyze the patents in suit from the point of view of a person of ordinary skill in the art in 1994?

A. Yes, I did.

Q. Were you a person with ordinary skill in the art in 1994?

A. I was.

Q. Dr. Grant what is the general subject matter of the patents in suit?

A. The general subject matter is the production and measurement of a low molecular weight form of copolymer-1.

Q. What is the low molecular weight form of copolymer-1 intended for?

A. That's intended for treatment of patients with multiple sclerosis.

Q. You said it was a low molecular weight of copolymer-1. What does the patent technique teach for measuring molecular weight of copolymer-1?

A. The patent teaches the use of size exclusion chromatography.

Q. Mr. Int-Hout, if we could put the cover of the '808 patent [191] on the screen. Let's look at the title. The title of all of the patents in suit, Dr. Grant is copolymer-1 improvements in compositions of copolymers. Could you tell us what a copolymer is?

A. Yes, but let me start with what a polymer is and then I'll go to what a copolymer is. I prepared a slide.

MR. JAMES: John, if you could put the first slide up, please.

Q. Dr. Grant, using this slide could you explain what a polymer is?

A. Yes. First of all, this slide shows a series of circles or spheres, if you will, that are hooked together by these gray bars and each of these spheres represents what we call a monomer. Mono

means one, of course. A polymer is simply many of these single monomers hooked together as depicted here. Poly, of course, means many.

Q. And in a polymer are all of the monomers the same?

A. Yes, they are.

Q. Could you contrast that with what a copolymer is?

A. Yes, on the bottom of the slide I have depicted a copolymer. You see it's very similar to a polymer that it has these monomers hooked together by these gray bars, but in this case colors of all these monomers are different and that just signifies that each monomer of a different color is a different substance and that's what a copolymer is. It's made up of [192] different monomers.

Q. What are the monomers that make up copolymer-1?

A. They're amino acids.

Q. Can you explain what an amino acid is?

A. Yes, sure. I have a slide. So this slide shows the basic chemical structure of an amino acid. If you look on the left-hand side of the blue box you'll see the N and the two H's. That stands for nitrogen, two hydrogen. Two atoms. That's called an amino group. Then if you look at the right side the red box you see the C, two O's and H, that's carbon, two oxygens and a hydrogen. That's called a carboxylic acid group or acid for short. So you put those two together, you get the amino and acid and the lines that connect these two together are called bonds.

Q. At the bottom of that amino acid there is an R. What is that?

A. That R represents another chemical structure that is different in each amino acid and serves to distinguish one amino acid from another.

Q. Let's move to the next slide.

A. So I guess the best way to show that is to look at the four amino acids that are in copolymer-1. The names are at the top there; glutamic acid, lysine, alanine and tyrosine. In the black structure that's the basic structure of the amino acid is [illegible]at I described in the previous slide and the colored letters [193] there such as CH^2 CH^2, carbons, hydrogens the O's are oxygen, those are different R groups. For each amino acid they have a different configuration or different structure.

Q. Dr. Grant, how are those amino acids hooked together in copolymer-1?

A. They're hooked together by peptide bonds.

Q. And what do you call a polymer that's hooked together with peptide bonds?

A. You call them polypeptide because there are many peptide bonds.

Q. Let's go to the next slide. Could you explain what's shown on this slide?

MR. JAMES: Your Honor, with your permission I'm going to approach and hand him a laser pointer.

THE COURT: Sure.

A. So what this slide shows is a short section of a polypeptide. If you notice that, let's just look at the

lower left hand part right here, this is the basic structure of an amino acid. We have four amino acids hooked together, they're hooked together by a peptide bond which is highlighted in yellow right here. We have many amino acids in this strain and we have many peptide bonds and that's what's constitutes a polypeptide.

Q. There's a lot of talk in this case about molecular weight. Could you use this slide just to describe the concept of [194] molecular weight for this molecule?

A. Sure. So the molecular weight of an amino acid or any molecule is simply the sum of the atomic weights of the atoms that it's composed of, so in this particular case if we look at the bottom left hand -- excuse me, right there, the bottom left hand amino acid, you'll see there are some carbon atoms, nitrogen atoms, some hydrogens and some oxygens. If you add up the atomic weight of all those atoms you get the molecular weight of all those acids. In turn, if you add up the molecular weights of all the amino acids you you'll get the molecular weights of the polypeptides.

Q. Where do you find the molecular weight of those atoms?

A. They're found in the periodic table of the elements.

Q. In copolymer-1 are all of the polypeptides the same length and sequence?

A. No, they're not. They're different lengths and different sequences.

Q. Let's look at the next slide. Could you explain what's shown in this slide?

A. This is just an illustration to illustrate the point that you just asked me about, and this just shows the various number of different polypeptides and I'm just depicting them like this by the stream of circles or stream of beads, if you will, and it shows that each one of them has a different length but in addition to that each one of them has a different sequence of [195] amino acids, which are shown by different letters which stand for glutamic acid, alanine, lysine and tyrosine.

Q. How would you refer to one of those polypeptides; what would you call that?

A. One of those polypeptides would be -- I'm not sure if I understand.

Q. I was just wondering if you could just refer to those as the individual polypeptides or species, if you would?

A. Excuse me. The individual polypeptides are often called species because they all have a distinct molecular weight.

Q. Dr. Grant, could you explain why the polypeptides in copolymer-1 vary in their length and sequence?

A. That's a consequence of the way that copolymer-1 is made.

Q. Did you create any slides and animations to help illustrate this point?

A. Yes, I did.

MR. JAMES: Your Honor, with your permission I'd like to ask Dr. Grant to come down to the screen and explain. If you could stand on the left side.

A. Okay, so we're starting out here with the mixture of these different amino acids; the glutamine acid, lysine, tyrosine, alanine. In this mixture there's a lot more than is shown on the slide, of course, basically thousands or millions of different amino acids and they're all in a vessel of some sort which would be like a flask or something like that and you'll [196] notice they all have this little loop on them right there. I kind of think it looks like a headphone, but what that loop signifies is that in their present form these amino acids are not able to join to each other yet.

And then we also have this other thing in here this yellow box with an I in it. That's called an initiator and that's another chemical, it's not an amino acid, but it's a chemical that can come in and join with one of these amino acids and when that happens, the polymerization or the growing polypeptide chain process begins. And I have an animation now that we can start to kind of demonstrate how that works.

Q. Before we do that, I had one question. The little loop you said looks like headphones, what is the chemical name for that?

A. That's an N carboxy dihydrate.

Q. So in copolymer-1 the polypeptides are made by polymerizing N carboxy dihydrate?

A. That's correct.

Q. Let's look at the animation.

A. Starting the animation, watch the initiator. It runs into an amino acid, stops right there. You see it hooked into the amino acid made the headphone disappear which means it's now capable of hooking to another amino acid which we've seen happen and its headphone also disappeared. So these are becoming what we call activated, which means they can join to other amino acids. If we keep the animation going, we see the [197] growing polypeptide chain occurring right here and eventually another initiator up here will come in and a new chain will start.

This process just keeps going on until another initiator comes in gets another amino acid and chains start growing and growing and growing until the reaction is finished and we end up with a mixture of a very, very large number of different polypeptides. And this mixture is non uniform with respect to the lengths of all polypeptides and with respect to all of the amino acid sequences in the polypeptides.

Q. Thank you, Dr. Grant. Now, are the chains that are shown in this slide the actual sizes of the chains in copolymer-1?

A. No they're not. This is just for illustration purposes. The chains themselves are much larger and also they're not, the chains don't have this straight rigid configuration that we've shown here either. That again is just for illustration.

Q. Thank you, Dr. Grant. You can return to the stand, please.

Dr. Grant, if you could turn to Plaintiff's Trial Exhibit 1 again in your binder, and Mr. Int-Hout if

you could bring up column 3, lines four through eight. Dr. Grant, on the screen we have column 3 of the patents in suit. Could you read the sentence that's highlighted there beginning at line 6?

A. It says, "The molecular distribution of the two batches was determined on a calibrated gel filtration column." Then it has Superose 12 in parenthesis.

[198]

Q. Dr. Grant what is gel filtration?

A. Gel filtration is just another word for size exclusion chromatography. They both mean the same thing.

Q. And what is a gel filtration column?

A. Well, a column is just the vessel in which the gel filtration or the size exclusion chromatography takes place. And I'll have a slide later on kind of showing what column it is.

Q. Dr. Grant, it says that the molecular distribution of the two batches was determined. What is the molecular distribution?

A. Molecular distribution is just a description of the molecular weights of the material that is in the mixture.

Q. When the patents were filed for, were there any other ways to measure the molecular weight distribution of copolymer-1 other than size exclusion chromatography?

A. No, I don't think so. In fact, I mean, I think size exclusion chromatography was and still is the

only and best way of determining the molecular weight distribution of a mixture of polypeptides.

Q. So let's look at the next slide. Dr. Grant, is this a slide that you created?

A. Yes, it is.

Q. Could you use this to describe size exclusion chromatography?

[199]

A. Yes. This slide then depicts that column we talked about just previously. And all this column is really is just a cylinder. It can be glass or it can be metal, but it's the vessel in which the chromatography itself takes place.

Q. Put up the next slide. Dr. Grant, this slide shows some little brown circles inside that column. What are those?

A. Those brown circles are called the separation gel. They are the actual solid or matrix, as we call it, that the separation of the polypeptides takes place on and in addition to that, we show that there's liquid there too. These beads are placed into the column in liquid.

Q. Dr. Grant, did you bring anything for show and tell today so you could show what those beads look like inside the column?

A. Yes, I did. Oh, there it is. Thank you. I brought a sponge. The beads in the slide look like they're solid, but in fact they're not. They're more like this sponge that has a lot of channels or pores in it, and what that does is if you have a large molecule, let's say, for instance, like the fist of my hand it's too

large to get into the sponge because it's much larger than these pores, but if you have a small molecule like the tip of my finger it can penetrate into these pores. That's how size exclusion chromatography works.

The molecules you're trying to separate can either get into the pores or they can't and that process gives you the separation. And I'll demonstrate in a minute how that happens.

[200]

Q. Thank you. Now, how is the sample introduced into the column?

A. It's just introduced into the top of the column by some method. You can use an injector or in this case we show it's just a pipette, which is basically like straw.

Q. What happens to them after they're introduced?

A. After the sample is introduced, you start the liquid flowing into the column and that brings the sample down through the column and as it goes through the column the large molecules separate from the small molecules as depicted here. You see the larger kind of purple-ish molecules are at the bottom, the very small red or brown molecules are at the top yet.

Q. Let's go to the next slide and the next one. Dr. Grant, we've shown two boxes out to the right on slide 15. Could you explain what those are?

A. Yes, this first box -- I'm laser challenged. This first box is just a blowup of the very small edge of

one of these beads. You can see the dark spots. These are the pores starting to appear. Now, if you take and blow up the edge of that you can see these here and these are the pores that are in this gel much more distinctly.

Q. Play the animation, John.

A. So this animation shows the molecules coming down and encountering these pores. I'll run it a couple of times. You [201] see the large molecules aren't able to get into the pores very well while the small molecules are. Let's go one more time. So the large molecules can't get into these pores, so they pass through very quickly, but the small molecules have to go into these pores and pass some time so they get delayed and as a result they come out much later than the large molecules and that's how size exclusion chromatography works.

Q. Okay, let's go to the next slide, Mr. Int-Hout. Maybe an animation. Yes, Dr. Grant, could you tell us what's shown on -- please stop that. Thank you. What's shown here, Dr. Grant?

A. So again we have a column with our gel matrix or beads inside and blind sample to the top and separation will take place. But now we have a tube that's connected to the bottom of the column and this tube is going over to an instrument that we call a detector and what this detector does, it senses the presence of these molecules and also the quantity or the weight of the molecule that's coming out of the column.

Q. All right, so let's let the animation run. Could you describe what's happening here?

A. So we see the separation process happening again. I'm having trouble with this pointer, I'm sorry. There it is. Molecules are coming out, they're passing this detector and the detector is sensing their presence.

Q. Now, let's go a little further. Stop right there. Doctor, [202] in this particular slide you've shown an XY coordinate in the upper left-hand corner. Could you explain what that is?

A. Yes. This is how we're going to record what the detector sees. So as the molecules pass -- let me talk about what the axis are first. The Y axis shown first is simply the amount of the material that's passing the detector and the X axis is labeled time and time goes from the left to the right so molecules are coming out of the column at different times because the big ones are not being delayed and the small ones are being delayed so as they pass the detector we'll record that on this graph here.

Q. Let's let that run.

A. This animation will show how that happens in an illustrated way. So as the molecules come out and they pass the detector here, you see that their presence is being sensed and the amount is being recorded and it gets up to a peak and then it starts going back down and at the end. When all the molecules are passed through we're back down to baseline.

Q. Dr. Grant, I notice that the big molecules came out first but the line only deflected a little bit where you have 25 minutes or so. Why is that?

A. That's because at this point in time the detector is not measuring the molecular weight of the molecule, it's just measuring how much of it is there, so even though the big ones are coming out, there may be at the very beginning only a small [203] amount of them.

Q. Now, this graph that you're showing in the upper left-hand corner, does it have a name?

A. Yes, it's called a chromatogram.

Q. Now, Dr. Grant, let's put up the next slide. And, John, if you could put in the curve. We were talking about a chromatogram. Could you describe for us or tell us what a chromatogram shows us?

A. Once again we have two axes on the graph, one, the Y axis, the amount of material that's shown by the detector and then on the X axis is the time, the times going from left to right. So those are zero time to however much time it takes to run the chromatogram.

Q. Does the chromatogram depict all of the molecules in the sample?

A. Yes, it does. You start out at the beginning with no molecules being detected. All molecules pass through. At the end there are no molecules being detected. That's 100 percent of the molecules going through that column.

Q. How do you determine the molecular weight of the molecules that are coming out and are shown on the chromatogram at any particular time?

A. Well, remember I said that the big molecules come out first or at an early time, the small

molecules at later time so you have to develop a key where you can correlate the time that [204] they come out of the column with the molecular weight.

Q. What is that key called?

A. The key is called a calibration.

Q. Was this idea of a calibration understood in 1994?

A. Yes, it was.

Q. I'd like to talk a little bit about how that calibration process is carried out. How do you create a calibration, Dr. Grant?

A. I'm going to illustrate that on the next slide. And what this slide shows labeled standards is another chromatogram. Again, we have the amount on the Y axis and the time is along the X axis going from left to right.

What this chromatogram shows is it shows five different substances that come out of this column and this substance right here comes out early and this substance on the right has come out late and these are called standards, and they're called standards because we've already determined what their molecular weight is. Okay? So if we know what their molecular weight is and you know what time they've come out of the column, we can plot that. And I show that at the bottom of the slide.

Now I'm plotting the molecular weight versus time and I just correlate the time that the molecules, the standards come out of the column and bring that down to the axis on the time and since I know the molecular weight I can go up on the Y [205] axis to

find that molecular weight and come over and produce a point. If I then do that for all of the standards, I produce a series of points and when I have all the points, I draw a line through there and this line is the calibration or the key that you use to determine molecular weight of your sample.

Q. Dr. Grant, how do you know the molecular weight of those standards?

A. You determine it by some other method besides size exclusion chromatography and there are several different methods that can be used.

Q. Dr. Grant, after you get your calibration, what do you do with it?

A. Once you get your calibration then you compare it to the chromatogram of your sample which I'm now showing again at the top of this slide. Again, just to reiterate, this chromatogram shows the amount of material and the time that these material comes out of the column, so if you want to find the molecular weights let's say of the peak up here, you find out what time it came out of the column, you correlate that to the time that's on your calibration curve down here -- I keep losing this, I apologize. Correlate it to the time of your calibration curve and then go over to the Y axis and you can read your molecular weight off directly. You can do that for any other point on the chromatogram. You can do it for a time early, time late, any time on that chromatogram and determine [206] what the molecular weight that has come out of that column is at any point in time.

Q. We come back to standards, what characteristics do you look for when choosing standards?

A. When you're doing what I call conventional chromatography, which is what I've been describing here, you look for standards that have the same size to molecular weight relationship as your sample does.

Q. Let's put up the next slide. Perhaps you can use this to explain that concept, Dr. Grant.

A. Okay, yes. This slide shows two polypeptides, shall we say, one on the left here, that's basically just a string and that string is relatively short. The one on the right is also a string, but you see that string is much, much larger. Now, both of these polypeptides have basically the same kind of confirmation that we call loosely coiled, you can see they're very loosely wound and what this means is that the large one on the right having much bigger size will come out of the column earlier than the smaller one on the left, even though they're the same type of confirmation or coil, if you will.

Q. Dr. Grant, those molecules shown on the screen, they look flat. Are they flat?

A. No, they're actually three dimensional. If you can draw a circle around them, kind of show their circumference and then imagine that's not a circle but a sphere. It's in three [207] dimensions and you can turn it around, see it has three dimensions and that's what a molecule basically looks like in solution.

Q. That volume that the molecules have in solution, what is that called?

A. That's called a hydrodynamic volume.

Q. Was the concept of hydrodynamic volume well known in 1994?

A. Yes, it was.

Q. So Dr. Grant, let's look at the next slide and here we show something called a tightly coiled standard in the center. Can you explain what's shown on here?

A. Yes. In the center of this tightly coiled standard, although you can't really see, is a very, very long string, but it's all tightly coiled, wrapped up very tightly, but you see by drawing your circle around here and imaging it as a sphere they both have the same size, even though they don't have the same length or the same molecular weight, if you will. And what this means is that even though they have the different molecular weight, if they have -- there we go, even though they have a different molecular weight, they have the same size, so they're going to come out of the column at the same time.

Q. And, Dr. Grant, if we look at the right side of the slide now and can you contrast that with the red standard in the middle and the larger peptide or the larger molecule on the right?

[208]

A. Yes. So the red molecule in the middle has a string, if you will, that's the same length as the green molecule on the right, but it has a different size, so even though they're the same molecular weight,

they'll come out of the column at a different point. That's opposed to the fact that the green molecule on the left is a much shorter length of fragment of string, but it's the same size, so even though it isn't the same molecular weight, it will exit the column at the same time. And what this underscores is the fact that you have to have the same size molecular weight relationship or volume to molecular weight relationship with your standards as you do for your sample in order for the size exclusion chromatography to work.

Now, I've been explaining conventional size exclusion chromatography. There's another type of calibration that you can do called universal calibration that doesn't require this relationship, but it uses a different physical property called viscometry that adjusts for it and gives you accurate molecular weights also. There's two types of calibration that can be used.

Q. With respect to what you called conventional calibration, was the concept of matching the standards in the sample known to scientists in 1994?

A. Oh, yes, it was. I mean, in fact, when I was learning how to do size exclusion chromatography in the 1970's, it was one [209] of the very, very first things that I was taught.

Q. Now, Dr. Grant, do you have an understanding as to how many patents are being asserted by the plaintiffs against the defendants in this litigation?

A. Yes. There are nine.

Q. And have you examined the claims that are being asserted by the plaintiffs against the defendants?

A. I have.

Q. Have you prepared any slides categorizing the asserted claims of the patents in suit?

A. Yes, I have.

Q. Let's put up the next slide. Dr. Grant, can you explain how you categorize the claims?

A. I grouped them into three categories. The first is the average molecular weight and then the copolymer-1 molar fraction and then finally the TFA copolymer-1 molar fraction.

Q. We'll come back to average molecular weight in just a moment. Dr. Grant, can you explain what copolymer-1 molar fraction means?

A. Yes. Copolymer-1 molar fraction simply means that you can determine the number of molecules of any component in a mixture and determine whether or not their molecular weights are between certain bounds of molecular weight.

Q. And those are copolymer-1 molecules?

A. Yes, they are.

[210]

Q. What is the last bullet TFA copolymer-1 molar fraction? What does that refer to?

A. TFA copolymer-1 molar fraction refers to TFA copolymer-1, which is an intermediate on the way to making copolymer-1.

Q. What does TFA stand for?

A. That stands for trifluoroacetic.

Q. And is trifluoroacetic copolymer-1 used in the processes that are proposed by the defendants?

A. Yes, it is.

Q. Now, Dr. Grant, I'd like to go and focus on the average molecular weight claim limitations. Have you created a slide that categorizes the average molecular weight limitations that you have analyzed?

A. Yes, I have.

Q. Let's look at the next slide. Dr. Grant, can you explain what's shown on this slide, please?

A. Yes. This slide shows the three limitations that we're going to be talking about today, as far as average molecular weight is concerned. They are at the top about 5 to 9 kilodaltons, and they're found in claim 1 of the '808 patent, that is found in claim 1 of the '808 patent and claim 1 in the '589 patent.

The next one is about 4 to about 9 kilodaltons. That's found in claims 1 and 6 of the '847 patent, and also claims 1, 8, 9, 12, 23, 30 and 31 of the '539 patent.

[211]

And the last category, the last claim is 6.25 to 8.4 kilodaltons, and that's found in claim 10 of the '539 patent.

(Continued next page)

BY MR. JAMES:

Q. Thank you. Dr. Grant, and you understand that the Court has construed the term average molecular weight, correct?

A. Yes, I do.

Q. Let's put up the Court's claim construction? Could you read that into the record, please?

A. Yes. It says that: The peak molecular weight detected using an appropriately calibrated suitable gel filtration column.

Q. Is this the definition of average molecular weight that you have used in rendering your opinions in this case?

A. Yes, it is.

Q. You understand that Sandoz and Momenta have filed an application with the FDA to sell generic form of Copaxone?

A. Yes, I do.

Q. And have you examined the documents that were submitted by Sandoz and Momenta to the FDA regarding that proposed product?

A. Yes, I have.

Q. Now based on your review, have you formed an opinion as to whether the generic Copaxone product proposed by Sandoz and Momenta meets the average molecular weight limitations of the asserted claims?

[212]

A. Yes, I have. And in my opinion both products produced by Sandoz and Momenta meet all of the molecular claims in the patents.

Q. Let's look at plaintiff's trial Exhibit 209 in your binder, Dr. Grant.

A. 209-R, okay.

Q. Yes, I believe in your binder you have the redacted form of 209. Do you recognize that document, Dr. Grant?

A. Well, it's got a blank page, but I see on the top it says elucidation of structure and characteristics. I think that is this, the ANDA, Sandoz's ANDA from the December of 2007.

Q. Okay. And could you look at the date in the upper right-hand corner? What's the date?

A. December 26, 2007.

Q. Now, did you rely on this section, of the defendant's ANDA of Sandoz, Momenta ANDA in rendering your opinions in this case?

A. Yes, I did.

MR. JAMES: And, your Honor, we like to offer into evidence plaintiff's trial Exhibit 209, the unredacted version of 209.

MR. ACKER: We do not object to the unredacted version being used, but just for the Court's purposes. Only the redacted version should be permitted into evidence.

THE COURT: Only the redacted version will be made [213] public.

MR. ACKER: Very well. That's fine. No objection, your Honor.

THE COURT: Okay. It's admitted.

(Plaintiff's Exhibit 209 received in evidence)

MR. JAMES: Thank you, your Honor.

Q. Now, Dr. Grant, let's turn to page 2017 in plaintiff's trial exhibit 209.

A. Okay.

Q. Do you have that?

A. Yes.

Q. Could you tell us what this section of the ANDA describes, Dr. Grant?

A. Yes. This is a section of the ANDA entitled molar mass Mp by SEC RI using peptide standards.

Q. Perhaps you could unpack that title a little bit for us; what does that mean?

A. Yeah. Well, the abbreviation Mp refers to peak average molecular weight. And then SEC, of course, is size exclusion chromatography. And RI stands for the type of detector that was used in this instance, it's a refractive index detector, excuse me. And then it says it is used peptide standards and these are synthetic poly peptides that have been produced for this purpose.

Q. And what have the peptide standards been used for?

[214]

A. They've been used to calibrate the column that's used to determine the molecular weight of the substance.

Q. Mr. Int-Hout, if you could pull up the introductory paragraph there. Dr. Grant, could you read the first sentence into the record, please?

A. Yes. The Copaxone package insert lists the average molecular weight of glatiramer acetate as 5,000 to 9,000 daltons.

Q. Did Sandoz and Momenta, did they set the average molecular weight 5,000 to 9,000 kilodaltons I'm sorry -- let me ask that again. Did Sandoz and Momenta set average molecular weight 5,000 to 9,000 daltons as a specification for their product?

A. Yes, they did.

Q. And, in your opinion, do Sandoz's and Momenta's ANDA batches meet that 5,000 to 9,000 dalton specification?

A. Yes, in my opinion both Sandoz and Momenta's batches meet that specification.

Q. Looking at the next paragraph down under analytical method, does this section of the ANDA indicate how Sandoz and Momenta measured the molecular weight of their product.

A. Yes. It says that they used size exclusion chromatography.

Q. Does it say what kind of columns they used?

A. Yes. They're listing TSK gel G 3,000 and G. 2,000 columns.

Q. What are those?

[215]

A. Well, those designations are just the manufacturer's names for these columns. But what they are are size exclusion chromatography columns that have been developed for the purpose of, among other things, separating polypeptides based on their molecular weight.

Q. And could you read the next sentence in that begins with nine peptide reference standards, could you read that into the record please, Dr. Grant?

A. Nine peptide reference standards with amino acid compositions consistent with glatiramer acetate covering the molecular weight range from 1,500 daltons to 12,000 daltons are used to calibrate the retention time axis in order to determine an accurate measurement of Mp.

Q. Now, do you have an opinion as to whether the peak molecular weight values determined by Sandoz and Momenta were detected using an appropriately calibrated suitable gel filtration column?

A. Yes, I do. I believe that the columns that they list here are suitable for that purpose, in fact developed for that purpose, and that the standards that they're using are standards that would give you an appropriate calibration of this column.

Q. And why do you believe those standards would give you appropriate calibration?

A. Well, there were synthesized specifically to be like [216] co-polymer-1. They have the same four amino acids. They have the same -- they have, in this case a nearly random sequence of amino acids, and they will, in my opinion they'll have the

characteristics that standards would have to have in order to accurately measure the molecular weight of the polymer-1?

Q. What characteristics would those be?

A. Same size to molecular weight relationship as co-polymer-1.

Q. And, Dr. Grant, could you turn to plaintiff's trial exhibit 349 in your binder?

A. Okay.

Q. I realize that is an redacted version of the exhibit. With that in mind, Dr. Grant, could you flip through it and tell me whether you can identify this document?

A. Lot of blank pages.

Q. Yes.

A. I think based upon the title of the document, elucidation of structure and other characteristics and some of the things that I see that are not redacted, that I have seen this.

Q. Perhaps you can look at page 17948.

A. Okay.

Q. Do you have that?

A. I do.

Q. You recognize that?

A. Yes, I do.

Q. Does this refresh your recollection that you relied on [217] plaintiff's trial Exhibit 349 in rendering your opinions in this case?

A. Yes. It's the same section of the ANDA that we looked at before, and if I recall, it was a later version.

Q. Did you rely -- you relied on this document in rendering your opinions, Dr. Grant?

A. Yes, I did.

MR. JAMES: Your Honor, we would offer into evidence plaintiff's trial Exhibit 349, in its unredacted form.

THE COURT: With the same understanding.

MR. ACKER: Yes, your Honor, that's fine.

THE COURT: All right, thank you. It's admitted.

(Plaintiff's Exhibit 349 received in evidence)

Q. Dr. Grant, looking at page 17948, in this later submission did Sandoz and Momenta change their protocol from measuring molecular weight from the way that they had reported it previously?

A. No, they did not.

Q. If you look at the page 17948 that you have open there, could you tell the Court what's found on that page?

A. Well, again, it's a section of the ANDA that's entitled more mass Mp by SEC RI using peptide standards.

Q. And I'd like you to look at one particular portion of the in -- the analytical method section, in that paragraph the could you pull that paragraph up.

[218]

A sentence we read a few minutes ago Dr. Grant, about the nine peptide reference standards and it says that they're used to calibrate the retention time axis in order to determine an accurate measurement of Mp; you see that?

A. I do.

Q. What does that mean to you, Dr. Grant?

A. Well, it means that they believe that these peptide standards that they were using had the same size molecular relationship as the substance they were measuring and that it would give you a very accurate measurement of what that molecular weight would be.

Q. What do you understand accurate to mean in this context?

A. I understand accurate to mean the fact that it will represent the actual, the real molecular weight of the product.

Q. Do you understand Sandoz's product to be non-uniform with respect to molecular weight in sequence?

A. Yes, I do.

Q. And if you look at page 17949, the next page, Dr. Grant, are there specific molecular weight values provided on that page?

A. There are.

Q. Turn to that page. And I'd like to focus first on table 21, Dr. Grant. What information is provided in table 21?

A. Okay, table 21 lists six lots of Sandoz's glatiramer acetate drug substance. It shows the name glatiramer acetate [219] on the left, in the middle shows the lot number, and on the right it shows the results of the analysis and lists the peak molecular weights in daltons.

Q. Dr. Grant, you mention this was a drug substance. What is the drug substance?

A. The drug substance is the active ingredients in their product.

Q. And can you, for the record, can you read in the peak molecular weights for those six lots of drug substance, please?

A. Yes. Starting from the top, we have lot 077K7277. It presents a mean or average molecular weight of 8,407. And that's from two determinations, that's what N equal two means.

Then lot 087K7253 presents a mean peak average molecular weight of 7,275, again from two determinations.

Lot number 029K7279 has a mean of 7,641 from two determinations.

Lot number 049K7275 has a single molecular weight listed of 6,977.

Lot number 049K7276 has a molecular weight of 7,366. And lot number 059K7275 has a molecular weight of 7,199.

Q. Thank you, Dr. Grant. I'd like to look now down, further down the page to table 22. Dr Grant, what information is provided in that I believe 22, of plaintiff's Exhibit 349?

A. This is a similar table. Now it lists two lots of [220] glatiramer acetate injection, which is Sandoz's drug product and also the peak average molecular weights that were determined for them.

Q. And what are those peak molecular weights?

A. For lot CT0743, it lists a mean molecular weight of 8,274 from two determinations.

And for lot CT0750, it lists a mean of 7,417 from two determinations.

Q. All right, thank you. Now, Dr. Grant, when it refers to glatiramer acetate there, do you have an understanding what that is or glatiramer acetate is; did Sandoz tell the FDA what?

A. They said it was co-polymer-1.

Q. Let's look in your binder at plaintiff's trial Exhibit 206.

A. Okay.

Q. Dr. Grant, can you identify that document?

A. Yes. This is again a portion of ANDA that deals with a draft of their package insert.

Q. And is this a document that you reviewed in rendering your opinions in this case?

A. Yes, it is.

Q. Dr. Grant, I'd like to look under description. Could you read in the first part of the first sentence under description?

A. Yes. It says, "glatiramer acetate, in parentheses, formerly known as co-polymer-1.

Q. What does that convey to you, Dr. Grant?

[221]

A. That conveys to me, excuse me, conveys to me that Sandoz thinks that their product, glatiramer acetate, is co-polymer-1.

MR. JAMES: And, your Honor, we would offer into evidence plaintiff's trial exhibit 206?

MR. ACKER: No objection, your Honor.

THE COURT: Admitted.

(Plaintiff's Exhibit 206 received in evidence)

Q. Dr. Grant, could you turn in your binder to plaintiff's trial Exhibit 351, please. I recognize what you had in your binder is redacted, but, Dr. Grant, can you look at that and tell me if you recognize plaintiff's Exhibit 351?

A. Yeah. From the top part of the first page it's another portion of the ANDA that deals with batch analysis.

Q. Did you rely on plaintiff's trial Exhibit 351 in rendering your opinions in this case?

A. Yes, I did.

MR. JAMES: Your Honor, we would offer into evidence plaintiff's trial Exhibit 351?

MR. ACKER: No objection, your Honor.

THE COURT: All right, admitted.

(Plaintiff's Exhibit 351 received in evidence)

Q. Dr. Grant, if you look at tables two and three of plaintiff's trial Exhibit 351, what information is provided in those tables? That's on pages, for the record, 18608 through 18611.

[222]

A. Okay. The Copaxone that I have shows a portion of a table. The rest of it has been redacted. That's labeled batch analysis for glatiramer acetate, and it lists several lots, and it -- two rows that are left in my binder are rows that deal with molar mass and amino acid composition.

Q. Okay, let's look at, in table two, the row labeled TP-116. Do you have an understanding what TP116 is, Dr. Grant?

A. It's the test method that they used to determine the molecular weight of their product.

Q. And under acceptance criteria, could you read into the record what that says?

A. Yes. It says Mp is greater than or equal to 5,000 daltons, and is less than or equal to 9,000 daltons.

Q. What does that convey to you, Dr. Grant?

A. Well, that conveys to me that they expect their product to be -- to have an average molecular weight, a peak average molecular weight between 5,000 and 9,000 daltons.

Q. Dr. Grant, what range of values are provided for the peak average molecular weights in table two of plaintiff's trial Exhibit 351?

A. The table lists five different lots, and the range of molecular weight values that are there are from 5,932 daltons, to 8,407 daltons.

Q. And if we look at table three, Dr. Grant, what information is provided under the row TP-116?

[223]

A. TP-116 once again provides peak average molecular weight determinations for one, two, three, four lots.

Q. And what are -- what's the range of values that's provided there?

A. The range of values here is 6,977 to 7,641.

Q. All right. Now, Dr. Grant, have you prepared a slide summarizing the peak molecular weight values that are reported in the ANDA for the various lots of Sandoz's glatiramer acetate?

A. Yes, I have.

Q. Let's look at the next slide, John. Dr. Grant, what is shown on this slide, slide 26?

A. Okay, this slide shows the peak average molecular weight values that we've just been talking about for the various lots. On the left-hand side the lot numbers are presented there, and then on the right-hand side the peak average molecular weights in daltons are listed.

Q. And, Dr. Grant, is this a slide that you created?

A. It is.

Q. Now, have you made a determination as to which average molecular weight claim limitations are met by these lots?

A. Yes, I have.

Q. Let's look at the next slide. Now, Dr. Grant, which of these lots satisfy the molecular weight

claim limitation of about five to about nine kilodaltons?

[224]

A. In my opinion, all of these lots satisfy that claim limitation.

Q. And for the record I've read that incorrectly. It's about five to nine kilodaltons; is that correct?

A. Yes.

Q. And let's look at the next part of this, Dr. Grant. Which of these lots meet the limitation of average molecular weight about four to about nine kilodaltons?

A. In my opinion, all of these lots meet that claim limitations.

Q. And looking at the last average molecular weight limitation, 6.25 to 8.4 kilodaltons. Dr. Grant, which of the lots meet that limitation?

A. In my opinion, all but one of the lots meet that claim limitation.

Q. And why did you leave that one lot out of your analysis?

A. I left that out -- didn't put a check mark there because the value of 5,932 does literally fall between 6.25 and 8.4 kilodaltons.

Q. Dr. Grant, do you have an opinion as to whether if Sandoz and Momenta used the process in their ANDA to make co-polymer-1 product, whether their product would fall within the average molecular weight claim limitations of the asserted -- in the asserted patents?

A. Yes. In my opinion, if Sandoz and Momenta uses the process [225] that's described in their ANDA, all of their products will meet all of these claim limitations.

Q. Dr. Grant, I'd like to look at the -- go back to the grouping of molecular weight limitations that we looked at earlier, come back to co-polymer-1 molar fraction. Could you explain again what co-polymer-1 molar fraction refers to?

A. Yes. Well, of course it refers to co-polymer-1, and molar fraction simply refers to determination of the number of molecules in this case that have a distinct molecular weight, species molecular weight, if you will, between an upper and lower bound of molecular weight.

Q. And could you turn in your binder to plaintiff's trial exhibit nine, that's a copy of the '098 patent. And if you could bring up claim one.

Dr. Grant, with respect to molecular weight, perhaps we could start with you reading into the record the highlighted portion of claim one of the '098 patent?

A. Okay. It says, over 75 percent of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of two kilodaltons to 20 kilodaltons, and less than 5 percent of the copolymers have a molecular weight above 40 kilodaltons.

Q. Okay. And what does it mean there that they, the copolymers in the mixture on a molar fraction basis have a molecular weight in that range?

[226]

A. Molar fraction again, referring to individual molecules. And if you remember, if you think about co-polymer-1 is a mixture, that mixture is composed of individual molecules. And each of these molecules have their own distinct molecular weight.

So what this is saying is that for co-polymer-1, the molecular weights of 75 percent of those molecules are between two and 20 kilodaltons, and the molecular weights of 5 percent of those molecules are above 40 kilodaltons.

Q. Now, Dr. Grant, did you create a slide showing which claims contain the co-polymer-1 molar fraction limitations?

A. Yes, I did.

Q. Let's go to the next slide. Dr. Grant, could you explain what's shown in slide 29, please?

A. Yes. It shows the four co-polymer-1 molar fraction limitation. The first one is over 75 percent, between two and 20 kilodaltons. And that is claims one to three of the '430 patent.

The second is less than 2.5 percent above 40 kilodaltons. And that's claims 8 and 30 of the 539 patent.

The next also is over 75 percent between two and 20 kilodaltons, and less than 2.5 percent over 40 kilodaltons, and that's found in claims 9, 10 and 31 of the '539 patent, and also claim 8 of the '098 patent. And then the last is over 75 percent between two and 20 kilodaltons and less than [227] 5 percent over 40 kilodaltons, and that is found in claim one of the '476 patent, claim one of the '161 patent, and claim one of the '098 patent.

Q. Thank you, Dr. Grant. Have you created a slide in order to try to illustrate for the Court what this molar fraction limitation actually means?

A. Yes, I have.

Q. Let's look at the next slide.

A. So once again we have a chromatogram. And just to remind you that this chromatogram, the big molecules come out early, the smaller molecules come out later. So I've depicted 40 kilodaltons as coming out first, then 20 and then two.

Chromatogram represents the amount of material that is found at any particular time which is along the X axis going from left to right. And as I said before, this chromatogram is composed of a very very large number of individual molecules. Each these molecules has a distinct molecular weight. And what size inclusion chromatography allows you to do is to perform the separation and determine how many of those molecules have molecular weight between any particular bounds, in this case I listed 40, 20 and two because those are the molecular weight within the claim limitations.

Q. All right, thank you. Now, can you just take the area under the curve under the chromatogram and determine the molar fraction that, the percentage on molar fraction basis, Dr. [228] Grant?

A. No, you can't do it that way.

Q. Why is that?

A. It's because the curve as shown here is basically linear scale and the relationship between time and molecular weight is a log scale. So by

merely taking the area under that curve is going to distort the results.

Q. Dr. Grant, did you create a slide in order to illustrate how you calculated the molar fractions?

A. Yes, I did.

Q. Let's go to the next slide. What is shown on slide 31?

A. Well, so what I've done with this slide to illustrate this is to just show that the chromatogram is divided into a bunch of different segments or slices, as we call them. And these are just small rectangles. And each one of these rectangles, the area within the rectangle represents a certain amount of material. And then what you need to do is you need with your calibration curve to assign molecular weight to each of these slices. And then when you assign molecular weight to each of the slices, you can divide the amount of material by the molecular weight to give you the moles of material in each slice.

Q. What are moles?

A. Moles are just a measure of the number of molecules that are present.

[229]

Q. So I just want to make sure I understand. Each little rectangle represents an amount of material

A. Yes.

Q. -- coming out?

A. That's correct.

Q. And then you assign it a molecular weight?

A. That's correct.

Q. And then what do you do with those two values?

A. Well, as I said, once you assign the molecular weight, you can divide the amount by the molecular weight to give you moles.

Then between any two bounds, for instance, the two kilodaltons and the 20 kilodaltons that you have here, you can add up all of those moles. And if you then compare that to the total number of moles of the whole chromatogram, you will get a percentage value for the fraction of the number of molecules that are between these two molecular weight bounds.

Q. Dr. Grant, did you create a slide to show the mathematical calculation that you used to calculate the percentage?

A. Yes, I did.

Q. Let's look at the next slide?

A. So this just shows the math, it's very simple. On the top it's shown that you determine the number of molecules between two kilodaltons and 20 kilodaltons, and divide that by the total number of molecules in the entire chromatogram, and just [230] multiply by 100 percent. You get the percent of molar fraction between two and 20 kilodaltons. Then a very similar manner on the bottom I show that if you determine the number of molecules greater than 40 kilodaltons, and divide that with a total number of molecules in the chromatogram, multiply by 100

percent, you get the percent mole fraction above 40 kilodaltons.

Q. Okay, thank you. Now, on the slide you have a number of molecules but a minute ago you said that you do some division and get the number of moles. What's the relationship between those two things?

A. Number of molecules and moles are basically the same thing.

Q. Now, did Sandoz and Momenta, did they provide you with the data necessary to determine whether the molar fraction claim limitations were satisfied by their product?

A. Yes, they did.

Q. In what form were those data provided to you?

A. They were provided to me on a secure flash drive in a software package called Empower.

Q. And using those data, did you analyze whether the product, the Sandoz proposed drug substance meets the molar fraction claim limitations?

A. Yes, I did.

Q. Now, in order do that, Dr. Grant, did you have to extract individual polypeptides from the samples and measure their [231] molecular weights in order to determine the molar fractions?

A. No, of course not. As I said before, you can't do that. But what size exclusion chromatography does for you is it gives you the ability to do basically the same thing. It separates the molecules based upon their individual sizes and allows you to calculate the

number of molecules that are between any molecular weight bounds.

Q. Size inclusion described in the literature for this purpose, that is determining the percent molar fraction of molecules above or below a particular molecular weight?

A. Yes, it is. It's been used by many many scientists for many many years for this exact purpose. And I said earlier it's probably -- it is the only method that we have that enables us to do this.

Q. Now, the data you were provided, was that a large amount of data?

A. Yes, it was. When we extracted it from the empower software and put it into an Excel spread sheet it was very, a lot of numbers of pages. I don't remember how many, but a lot.

Q. And did you work with anyone to perform the calculations Dr. Grant?

A. Yes. I worked with Dr. Paul Winter at Chemir Analytical Laboratories in St. Louis.

Q. What was Dr. Winter's involvement.

A. Dr. Winter was an expert in empower software, so he [232] assisted me in extracting the data and putting it into excel spread sheet and then he helped me make the calculations.

Q. Did Dr. Winter perform any independent calculations on the data?

A. No. He only did what I instructed him to do.

Q. Now, have you prepared a slide which shows a summary of the results of your calculations, Dr. Grant?

A. Yes, I have.

Q. Let's look at the next slide. Dr. Grant, could you tell us what's provided on slide 33?

A. Yes. It's a summary of the results that I produced from the data that was provided by Sandoz. It deals with five different lots, which are listed over on the left-hand side. Then middle column to the right has the results for the percent molar fraction between 2 and 20 kilodaltons. And then the last column on the right has the results for percent lower fraction above 40 kilodaltons.

Q. Dr. Grant, could you read the values for each lots into the records, please?

A. Yes. So for lot 077K7277, the molar fraction between two and 20 kilodaltons was greater than or equal to 91.99 percent and the molar fraction above 40 kilodaltons was less than or equal to 0.36 percent.

For batch lot, excuse me, [233] O87K7253, molar fraction between two and 20 kilodaltons was greater than or equal to 85 percent, and molar fraction above 40 kilodaltons was less than or equal to 0.28 percent.

For lot number 049K7275, molar fraction between two and 20 kilodaltons was greater than or equal to 90.82 percent, and the molar fraction above 40 kilodaltons was less or equal to 0.23 percent.

For lot number 049K7276, molar fraction between two and 20 kilodaltons was greater than or equal to 87.36 percent and percent molar fraction above 40

kilodaltons was equal to or less than, less than or equal to 02.24 percent.

And for the lot 059K7275, the percent molar fraction between two and 20 kilodaltons was greater than or equal to 88.83 percent, and the percent lower fraction above 40 kilodaltons was less than or equal to 0.25 percent.

Q. Thank you, Dr. Grant.

MR. JAMES: While you catch your breath and take a drink of water, your Honor, we would like to offer slide 33 under Rule 1006 as a summary of the calculations that Dr. Grant performed on the date data he was provided.

MR. ACKER: No objection.

THE COURT: Any objection? Admitted.

(Plaintiff's Exhibit 33 received in evidence)

Q. Dr. Grant, do you have an opinion as to whether Sandoz's glatiramer acetate drug product in drug substance satisfied molar fraction claim limitations?

[234]

A. Yes, in my opinion their drug substance satisfies all, all of these molar fraction claim limitations, excuse me.

Q. Let's put up the next slide. Dr. Grant, can you tell us -- there we go -- thank you, John -- which of the lots that you analyzed had over 75 percent on molar fraction basis of the copolymers between two kilodaltons and 20 kilodaltons?

A. In my opinion, all of the lots had that molar fraction.

Q. Dr. Grant, which of the lots had less than 2.5 percent on a molar fraction basis of copolymers above 40 kilodaltons?

A. Again, in my opinion all of the lots met that limitation.

Q. And how many of these batches, Dr. Grant, had both over 75 percent of the copolymers between two kilodaltons and 20 kilodaltons and less than 2.5 percent copolymers above 40 kilodaltons?

A. In my opinion, all of them had that limitation also.

Q. And finally for the record, Dr. Grant, which of the batches that you anaylzed had both over 75 percent on a molar fraction base copolymers between two and 20 kilodaltons and less than 5 percent copolymers over 40 kilodaltons?

A. In my opinion, all of the lots met that limitation.

Q. Dr. Grant, if Sandoz and Momenta make co-polymer-1 using the process described in their ANDA do, you have an opinion as to whether the product will meet the co-polymer-1 molar fraction limitations of the asserted claims?

A. Yes. If Sandoz Momenta used the process described in their [235] ANDA, all of their products will meet these molar fraction limitations.

Q. Let's look now at the last set of the molecular weight limitations, TFA co-polymer-1 molar fraction. And, Dr. Grant, just if you remind us very briefly

again what are, what is a TFA co-polymer-1 molar fraction?

A. TFA co-polymer-1 is an intermediate on the way to co-polymer-1. It simply has these trifluoroacetyl protecting groups on all of the lysine residues, and once again the molar fractions are the number of molecules of the components and mixture that would fall between any particular molecular weight boundary.

Q. Did you create a slide that shows for the Court illustrates what TFA co-polymer-1 looks like?

A. Yes, I did.

Q. Dr. Grant, what's shown here on slide 38?

A. So this slide just illustrates the short segment of co-polymer-1 made up of the four different amino acids, glutamic acid, lysine alamine and tyrosine. And on the lysines, those are the ones with the Ls, we see those little blacks boxes, and those black boxes represent the trifluoroacetyl group.

Q. Does the trifluoroacetyl group have a known molecular weight?

A. Yes, it does.

[236]

Q. Let's look at claim one of the '430 patent. That's PTX-4, Dr. Grant. And if we could look at claim one, Mr. Int-Hout. Dr. Grant, with respect to the trifluoroacetyl co-polymer-1 molecular weight limitation, what does claim one of the '430 patent require?

A. It requires that over 75 percent of the molecules in trifluoroacetyl co-polymer-1 are within the molecular weight range of about two kilodaltons to about 20 kilodaltons.

Q. And did you create a slide that summarizes which of the claims, the asserted claims of the patents in suit have this trifluoroacetyl co-polymer-1 limitation?

A. Yes, I have -- I did.

Q. Let's look at the next slide. Dr. Grant, could you explain for the Court slide 39, please?

A. So this is the, that molecular weight limitation or, excuse me, that mole fraction limitation that we just saw in the patent. It states trifluoroacetyl l co-polymer-1 having over 75 percent of its molar fraction within the molecular weight range of about two kilodaltons to about 20 kilodaltons, and that's found in claims one to three of the '430 patent, claim one of the '476 patent, and claim one of the '161 patent.

Q. Thank you. Now does the synthetic group used by Sandoz and Momenta, does it make use of trifluoroacetyl co-polymer-1?

A. Yes, it does.

Q. And were you able to calculate the molar fraction of Sandoz [237] and Momenta's trifluoroacetyl co-polymer-1 intermediate as used in the manufacture of their product?

A. Yes, I was.

Q. And what data were your calculation based on?

A. It was based upon the data that was supplied to us on the secure flash drive.

Q. Are those the same molecular weight distribution data you were provided for co-polymer-1?

A. Yes, they are.

Q. Was Dr. Winter involved in these calculations, Dr. Grant?

A. Yes, he helped me.

Q. And what was his involvement in this calculation?

A. His involvement was exactly the same involvement that he had in the previous calculation. I told him how to extract the data and to -- what calculations to do on it.

Q. Did he perform any independent calculations on his own data?

A. No, he didn't do anything other than what I instructed him to do.

Q. Now, very briefly, Dr. Grant can you explain how you calculate the TFA co-polymer-1 molar fraction from the co-polymer-1 distribution data?

A. Yes. If you recall that slide that we just had up, that small string of co-polymer-1 with the TFA on the lysine groups, the TFA has a discreet molecular weight. So from the mole [238] ratio of, or the mole fraction of the co-polymer-1 substance, we can determine how many lysines are in there and we can then determine how many TFA lysines would be in there, and that would allow me or allow us to just

to have a simple conversion factor to convert the molecular to co-polymer-1 to the molecular weight of TFA co-polymer-1.

Q. And so if I understand correctly, the amount of TFAs related to the amount of lysine in the co-polymer-1?

A. That's correct.

Q. And, how did you determine the amount of lysine in Sandoz Momenta products?

A. The ANDA gave us the numbers for the mole percentage of lysine in their products.

Q. Now, did you create a slide that shows the molecular weight values that you calculated for Sandoz's trifluoroacetyl co-polymer-1?

A. Yes, I did.

Q. Let's look at the next slide. Dr. Grant, could you explain what's shown on slide 40, please?

A. Yes, this is a summary of the results of my calculation. On the left-hand side are the different lots that we performed our calculations on, and on the right-hand side under the heading percent TFA molar fraction between two and 20 kilodaltons are the values that I determined the percentage.

Q. Okay. And, Dr. Grant, what's the range of values for the [239] percent TFA molar fraction between two and 20 kilodaltons?

A. As shown on this slide, the range of values were between greater than or equal to 89.69 percent and greater to or equal to 92.82 percent.

MR. JAMES: And, your Honor, we would offer this slide as evidence under Federal Rule 1006 as a summary of the calculation that he performed on the data.

MR. ACKER: No objection, your Honor.

THE COURT: All right admitted.

(Plaintiff's Exhibit 40 received in evidence)

Q. Dr. Grant, have you made a determination as to which of the trifluoroacetyl co-polymer-1 limitations are met by Sandoz's product?

A. Yes, I have.

Q. Let's look at the next slide. Dr. Grant, could you explain what's shown here, please?

A. Well, again, this is just the data that we had on the previous slide. It shows the lot numbers, it shows the results of my calculations, and then on the very far right-hand column, excuse me, it shows the molar fraction claim limitation that applies.

Q. So which of the lots that you analyzed meet the trifluoroacetyl co-polymer-1 claim limitation of the asserted claims?

A. In My opinion, all of these lots meet that claim.

[240]

Q. Now, Dr. Grant, do you have an opinion as to whether if Sandoz and Momenta used the synthetic process outlined in their ANDA to make glatiramer acetate, whether it would produce an intermediate that satisfies the TFA copolymer-one molar fraction limitations?

A. Yes. If Sandoz meant to use the process outlined in their ANDA, all of their product would meet the claim limitation shown here.

Q. Now, Dr. Grant, let's turn to the analysis of the Mylan and Natco product. Have you reviewed Mylan and Natco's submission to the FDA regarding their product?

A. Yes, I have.

Q. And have you formed an opinion as to whether the generic Copaxone that's proposed by Mylan and Natco meets the average molecular weight limitations of the asserted claims?

A. Yes, I have. It's my opinion that their product meets the average molecular weight certification of the claims.

Q. Dr. Grant, could you turn to plaintiff's trial exhibit 318 in your binder.

A. Okay.

MR. JAMES: Your Honor, I just want to say we're at a sort of a natural stopping point here. We're going to go through the Mylan data. It will go faster than the Sandoz analysis, but it will go on for a little while. Would you like to for me to continue to the end or would you like to pick this [241] up in the morning?

THE COURT: It looks like everybody's tired.

MR. JAMES: I believe that's my fault.

THE COURT: Well, we'll adjourn then and we can start up with Mylan tomorrow.

MR. JAMES: Thank you, your Honor.

THE COURT: 9:30.

(Adjourned to September 8th, 2011 at 9:30 a.m.)

[Excerpt from the September 15, 2011 Trial Testimony of Carl J. Scandella, Ph.D.]

[1193]

Scandella – direct

this case of cop-1, there's actually no method known that, that will definitely give the right answer.

There are a few methods that are called absolute methods that will -- that can or are capable of giving the right answer, but that doesn't mean they will give the right answer in every case.

So for a large complicated molecule like cop-1, the meaning of molecular weight becomes fuzzy. One has to specify what method one is going to use to measure molecular weight, because different methods will give you a different answer, as is seen in the cop-1 case.

Q. And you've mentioned cop-1 a couple of times. In what capacity are you familiar with copolymer-1?

A. I'm familiar with copolymer-1 as an expert witness in this case. I was asked to review the Teva documents relating to this, and that's what I've done.

Q. Did you work with copolymer-1 before your work on this case?

A. No. Copolymer-1 was not available commercially until after 1995, and neither I nor anyone else had, except Teva, had experience with copolymer-1 at that time.

Q. How long have you been working on this case?

A. Almost two years.

Q. Do you believe that the molecular weight of copolymer-1 should be treated as an average molecular weight?

[1194]

A. Yes, I believe it has to be treated as an average molecular weight.

Q. Why is that?

A. For the reasons that I stated, that we don't know the chemical structure of the individual atoms or the individual molecules that make up cop-1, and so we can't simply calculate based on the chemical structure. And there is no way, even in principle, to measure each of the -- to measure the molecular weight of each of the molecules by mass spectrometry, for example. So we have to deal with the average for the collection of cop-1 molecules.

Q. Are you familiar with the number of possible different sequences in a sample of copolymer-1?

A. This is an interesting point, that the -- because of the size of copolymer-1, and the fact that there are many possible, possible monomers at each position of the chain, and there is around 70 positions, the number of possible sequences of cop-1 is — I've heard the number ten to the 29th, and that's an incredible number. None of us has any experience with a number that big. Chemists like to think in terms of a mole of something, but a mole of something is about ten to the 23rd molecules, and that's still a million times smaller than ten to the 29th. And I've heard that the number of stars in the universe is ten to the 22nd, and that's ten million times smaller

than the number of cop-1 structures calculated -- number of cop-1 [1195] structures calculated.

So we're dealing with an incredibly large number of structures. And, for all practical purposes, it's an infinite number. There's nothing we can do to make this, this large number of molecules countable or measurable individually.

Q. Are there different types of average molecular weight?

A. Yes, there are.

Q. What are they?

A. The most commonly used types of average are number average, weight average, Z-average, and sometimes people use viscosity average, which is still another kind.

Q. What about peak molecular weight?

A. Well, in my opinion, the term peak molecular weight describes a single point on the chromatogram, and not -- so it's not a true average. It's just where the peak occurs. It has been used as so-called peak average in the Teva literature, and in the reports that have gone back and forth about this molecule. But, in my opinion, it is not a true, not a true average.

MR. JAMES: Your Honor, I think what we're talking about here is claim construction again. And as your Honor knows, we've had two hearings on that and your Honor's rendered a claim construction order. So I would just object to testimony that's just going back to rehash the claim construction issues.

[1196]

MR. AANNESTAD: Your Honor, we're not trying to rehash construction issues. He's going to be talking about these values during the day, and that's the only question on it and I just want to be clear for the record.

THE COURT: All right. Go ahead. That's fine.

MR. AANNESTAD: If we could put up slide three, please.

Q. Is this a slide you helped prepare?

A. Yes, it is.

Q. What does this show?

A. Well, the purpose of this slide is to illustrate that for a particular sample of a copolymer -- we were calling it sample A in this test tube -- there are several molecular weight averages that can be associated with that polymer. And on the top I've shown the number average, the viscosity average, the weight average, and the Z-average, and underneath I've indicated the peak average for the reason that I explained.

Q. For a given sample with a distribution of molecular weights, are the different types of molecular weights typically the same?

A. Well, unless the molecule is a single species, the different types of averages will be different, the numerical value will be different.

Q. What is the general relationship among the different types of molecular weights for complex polymers?

[1197]

A. By their definition, the number average is the lowest, the weight average is larger than the number average but smaller than the Z-average, and the Z-average is the highest.

The viscosity average is somewhere -- it may be close to the weight average or maybe not. And the peak average doesn't bear a definite relationship to these, but it's often it's usually between the number average and the weight average.

Q. Will different analytical techniques yield different types of average molecular weight?

A. Well, in principle, they would all yield the same value. But when you get into this region of very complicated samples, they often don't yield the same value. And as we're going to see later for cop-1, they don't yield the same value for cop-1. Excuse me.

Q. What are the various types of molecular weights that you can get from size exclusion chromatography?

A. One can get number average, weight average, and Z-average from -- and peak average from size exclusion chromotography.

MR. AANNESTAD: Could we move to the next slide.

Q. I like to talk to you about a little bit more about size exclusion chromotography or SEC.

We've heard a lot about SEC in this trial. Could you please describe how it works in your own words?

MR. AANNESTAD: And, your Honor, if I may approach the witness, I have -- Dr. Scandella had

requested for this he

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[Excerpt from the September 16, 2011 Trial Testimony of Carl J. Scandella, Ph.D.]

[1227]

* * *

Scandella – direct

Q. Do the asserted patents in this case disclose how to measure the weight of copolymer-1 in order for one to practice the claim limitation?

A. Yes. They specify that the molecular weight should be measured by size exclusion chromatography on a Superose 12 column, on a calibrated Superose 1 column.

* * *

[1256]

* * *

Q. What type of average molecular weight does a viscoscity measurement provide?

A. Viscosity measurement provides its own type of average, called a viscosity average.

Q. And what types of average molecular weight can you get from ultracentrifugation?

A. Depending on how it's done, ultracentrifugation can yield a Z-average or a weight average.

Q. And you've already discussed which types of molecular weight you can get from a Superose 12 size exclusion

[1257] chromatography, correct?

A. The Superose 12 size exclusion chromatography averages are peak average molecular weights.

Q. As listed here?

A. As here, yes.

* * *

[1314]

* * *

Scandella – cross

Q. All right. So now, Dr. Scandella, size exclusion chromotography was first described in the literature in 1960's, correct?

A. About then, yeah. I think it was actually little earlier than that, but that's about right.

Q. And size exclusion chromotography was well known in the scientific literature in 1994, correct?

A. Yes, it was.

Q. And there were many publications describing the use of size exclusion chromotography as of 1994, correct?

A. Correct.

* * *

[September 19, 2011 Trial Testimony of Gregory A. Grant, Ph.D.]

[1397]

* * *

Grant – direct

MR. JAMES: Plaintiffs recall Dr. Gregory Grant.

THE COURT: All right, Dr. Grant. Good morning. And you're still under oath, Dr. Grant.

GREGORY GRANT, called as a witness by the Plaintiff, having been previously duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. JAMES:

Q. Good morning, Dr. Grant.

A. Good morning.

Q. Were you in the courtroom for the testimony of Dr. Scandella?

A. Yes, I was.

Q. Did you hear his testimony that the patents in suit failed to provide sufficient information to accurately determine the molecular weight of copolymer-1?

A. Yes, I did.

Q. Do you agree with that?

A. No, I do not.

Q. Do you have an opinion as to whether a person of ordinary skill in the art would have been able to

determine whether a given copolymer-1 sample met the molecular weight limitations of the asserted claims based on the teaching of the patents in suit?

A. Yes, I do. I believe they would have been able to do that [1398] based on the patents in suit.

Q. Do you have an opinion as to whether that determination would have required an undue or excessive amount of experimentation?

A. Yes. I don't think that would.

Q. Let's look at PTX 1, that's the '808 patent, column 3. We put up column 3, lines 6 through 8.

MR. ACKER: If I may interrupt, do you have a binder for us?

MR. JAMES: I believe they were handed out.

Q. Now, before we talk about this sentence, Dr. Grant, could you remind us about your opinion of the relative level of skill of the art of the patents in suit?

A. Yes. I think that the relative level of skill is very high, and that a person of skill would need to have extensive experience in size exclusion chromatography, especially as it applied to polypeptides.

Q. And this sentence says that the molecular distribution of the two batches was determined on a calibrated gel filtration column Superose 12. Did you hear Dr. Scandella testify that the patent is not enabled because it fails to disclose the method of calibration?

A. Yes, I did.

Q. Do you agree with that opinion?

A. I do not.

[1399]

Q. And can you remind us again, briefly, Dr. Grant, what calibration is?

A. Calibration refers to the use of materials called standards, who have had their molecular weight determined and calibration concerns observing the behavior of these standards on the column and recording the time that they come out of the column.

Q. And did you hear Dr. Scandella testify that protein standards would be appropriate standards for copolymer-1?

A. Yes, I heard that.

Q. Do you agree with that, Dr. Grant?

A. I do not.

Q. Can you explain why?

A. Because protein standards do not have the same size as the molecular weight relationship as copolymer-1 does, therefore they give erroneously high values and they're simply not appropriate for that reason.

Q. Now, what methods of calibration were available in 1994 to accurately determine the molecular weight of copolymer-1?

A. Do you have that slide to put on?

Q. Yes, you have a slide that you created. Put up the first slide?

A. Yes, I listed the appropriate types of calibration that were available. The first one is the self-

standard calibration, and that simply means that you use standards that [1400] are the same material as the substance you want to analyze, in this case copolymer-1 and there's two ways to attain those standards. One is to make a wide, a batch that has a wide molecular weight distribution and fractionate it by dividing it into smaller pieces that have differing molecular weights.

The other way is to use what we call whole polymer standards and that is simply to use the standards that are synthesized in a particular step and use the whole material that is produced. And then finally there's also what we call universal calibration, which as I mentioned last week in my testimony, does not require that the size to molecular weight relationship is the same, because it uses another physical principle that compensates for that.

Q. What is that physical principle?

A. Viscosity. Intrinsic viscosity.

Q. Looking at the two bullets under self-standard calibration, the first one is fractionated standards. Was fractionation known in the art in 1994?

A. Oh, yes, it certainly was.

Q. Is it described in the patent for copolymer-1?

A. It is.

Q. What were the techniques that were available in 1994 to fractionate samples like copolymer-1?

A. Well, in this context what was used is size exclusion chromatography.

[1401]

Q. How would you use size exclusion chromatography in order to fractionate a sample?

A. Remember that size exclusion chromatography separates molecules based upon their size, the larger one comes out of the column first and the smaller ones come out later, so if you collect fractions in a test tube as the molecules are coming out the column, you can separate from one tube to another molecules of different sizes.

Q. The whole polymer standards, Dr. Grant, was that described in the literature in 1994?

A. Yes, it was.

Q. We'll come back to universal calibration in a little while, but can you describe the state of the literature on universal calibration in 1994?

A. In 1994, there was extensive literature on universal calibration and a very large number of studies that showed that it worked quite well for a whole variety of different types of polymers.

Q. Did you hear Dr. Scandella testify that a person of skill would not have chosen self standards for copolymer-1 because developing them would have been a major research project?

A. Yes, I did.

Q. Do you agree with that testimony?

A. No, I do not.

Q. Can you explain why?

[1402]

A. Well, because I think that, for instance, the patents in suit and the literature previous to that explain very well how one would make copolymer-1, and that information can be used to produce self standards.

Q. Now, as far as fractionation goes, what kind of work would be involved in fractionation?

A. It wouldn't be very difficult at all. You simply set up a size exclusion chromatography column, load your sample on to it and collect fractions in a test tube.

Q. Now, once you had the self standards in hand, Dr. Grant, how would a person of skill in the art have used those to calibrate the column?

A. Well, they would have determined the molecular weight characterizations of the self standards and they would have run those standards on the column, recorded where they came out of the column and then made the calibration plot that correlated their molecular weight to their retention time or their elution time from the column.

Q. What were some of the techniques available in 1994 to measure the molecular weight of the self standards?

A. There were several. For instance, there was multi angle light scattering, there was viscosity measurements, there was ultracentrifugation, there was mass spectrometry. I might have missed one or two, but there were several.

Q. Were all those techniques that you just named, were they [1403] well known in the art in 1994?

A. Yes, they were.

Q. Did you hear Dr. Scandella testify that depending on the molecular weight technique that you used to measure your standards, you would get a different calibration curve?

A. Yes, I heard that.

Q. Do you agree with that testimony?

A. No, I do not.

Q. Why not, Dr. Grant?

A. Because the literature has numerous examples of procedures that are used to resolve calibration curves that are produced by different molecular weight measurements into a simple calibration curve.

Q. Okay. Let's put up on the screen slide 16 from Dr. Scandella's presentation? And, Dr. Grant, can you briefly remind us what's shown in slide 16?

A. Well, what's shown here on the top of the slide is a chromatogram, a broad chromatogram, and below that are shown standards that have much more narrowed molecular weight distribution, and then the standards are given molecular weight values determined by three different methods, in this case ultracentrifugation, mass spectrometry, osmometry, and the number indicates that each method produces a different molecular weight value for each of the standards, and then at the bottom is plotted a calibration curve where all of the [1404] molecular weights are plotted in relation to the peak time of the standards.

MR. JAMES: Your Honor, with your permission I think it might make sense for Dr. Grant to come out of the witness box to explain the next few slides.

THE COURT: Sure. That's fine.

Q. Dr. Grant, the three techniques that are listed there in that slide, ultracentrifugation, mass spectrometry and osmometry. Can you explain at what time point they're applied for each standard?

A. In this figure they're applied all at the same time point and that's peak time of the standard in every case.

Q. Would it be appropriate to apply all of these molecular weights to the same time?

A. No, it would not.

Q. And why is that?

A. Well, because the molecular weights do not correspond to molecular weights in the chromatogram that come out at the same time. The individual different molecular weights corresponds to different times in the chromatogram.

Q. Do you have a slide that would help illustrate that?

A. Yes, I do.

Q. Let's put up PTX 982. What is this, Dr. Grant?

A. This is a slide from last week. It shows a chromatogram, and then designated on the chromatogram are shown the times [1405] that correspond with the various different average molecular weights that can be determined from the

sample that is being run through that chromatogram.

For instance, we know the peak average molecular weight is at the peak of the chromatogram, but once you calculate the weight average molecular weight or a Z-average molecular weight or a number average molecular weight that molecular weight corresponds to the molecular weight in the chromatogram at a time different than the peak.

Q. Do you agree generally with the location and order of these average molecular weights indicated on this chromatogram?

A. Yes. Generally they're in the correct order that one would expect for a chromatogram of this type.

Q. Okay, now, let's go back to slide 16 from Dr. Scandella's presentation. And if this were done correctly, Dr. Grant, can you explain what would have happened or what we would see in those calibration curves?

A. If this was done correctly what we would see is that the molecular weights corresponding to let's say weight average would be over on this side so this calibration curve would have to shift over and the molecular weights corresponding to number average would be on the right side of this standard so this calibration curve would have to switch in the opposite direction and the end result would be if done correctly they would end up becoming the same calibration curve.

[1406]

Q. Did you create a graphic to explain this adjustment, Dr. Grant?

A. I did. So this is a slide similar to the one we've seen just previously. We have a chromatogram on the top. Here we show a chromatogram of five standards and below we have a calibration curve. In this particular instance this calibration curve represents the peak molecular weight so you see the time that the peaks or the standards come out we have points on the curve, on the calibration curve.

Q. Thank you. In this slide you show the standards a little bit broader, they're a little bit broader than the last slide we saw. Why is this?

A. This depicts I think more accurately self standards which are broader in molecular weight distribution than less polydispersed standards.

Q. By that you mean self standards for copolymer-1?

A. I mean self standards for copolymer-1, yes.

Q. Now, what would happen if you measured the molecular weight, then, by some absolute technique and calibrated the chromatogram?

A. Well, if you measured the molecular weight let's say by light scattering, which is an absolute technique that gives you weight average molecular weight and if you were to assign it to the peak of the standard, you would get a different calibration curve. But there is another step that's involved that we [1407] haven't discussed so far which is covered quite extensively in the literature as of 1994 that allows you to take a molecular weight that does not actually occur at the peak but occurs someplace else and calculate an accurate molecular weight for the peak.

What that does is it would move, then, this calibration curve to be superimposed on this one.

Q. Let's look at the next part of the slide, Mr. Int-Hout. You put up a line that says "osmometry" What is that?

A. That is another technique of determining molecular weight. In this case it determines number average molecular weight. Remember from the previous slide the number average molecular weight would be depicted by a molecular weight on this part of the standard chromatogram, so rather than assigning the molecular weight determined to the peak, which is incorrect, you have to assign it over to this position right here and then you can go through the process described in the literature and it would move this peak over and superimpose it on to the peak molecular weight.

Q. Let's move to the next slide.

A. Here I'm demonstrating what this process involves. The arrows indicate the way in which the green calibration curve is going to move and as you see, when that happens, the molecular weight is now in that part of the marker where it's supposed to be for weight average molecular weight prior to the peak.

Q. And why is the weight average molecular weight line [1408] crossing on the left side of each of the standard chromatograms as you depicted it there, Dr. Grant?

A. Because that time corresponds to the weight average molecular weight that was determined for that standard.

Q. And why is that time before the peak?

A. Because the weight average molecular weight for chromatograms of this type is larger than the peak molecular weight.

Q. Let's go to the next part of the slide.

A. Now, this demonstrates the same process for the number average molecular weight as we saw on the previous slide, the number average actually corresponds to a time, its molecular weight corresponds to a time on this side, so the process following the literature would shift the peak calibration curve in this direction and you see now that the molecular weight, the number average molecular weight is now corresponding to a different time on the chromatogram as it should and the end result is that all three calibration curves become one.

Q. Just one more time, Dr. Grant. For the osmometry, the number average molecular weight, you show this little dotted line crossing on the right side of the peak or to the right of the peak for each standard. Why is that?

A. That's because the molecular weight that's determined by osmometry is smaller than the molecular weight at the peak.

Q. And, Dr. Grant, this process of obtaining a calibration [1409] curve from these different kinds of molecular weights, was this described in the literature in 1994?

A. Yes. It was described in a number of different places in 1994.

Q. Now, so, Dr. Grant, at the end of the day, what does all of this mean?

A. At the end of the day, what this means is that you in fact do not have three different calibration curves from which you have to choose which one to use. You in fact have only a single calibration curve that gives you only a single accurate value for the peak of the chromatogram.

Q. And how do you use that, Dr. Grant?

A. You use that as you use a regular calibration curve. You locate the time of the peak, come down, find that time on your calibration curve and you go over and read the molecular weight.

Q. Thank you, Dr. Grant. Dr. Grant, when was size exclusion chromatography first described in the literature?

A. It was in the late 1950's, early 1960's.

Q. And by 1994, what was the state of the literature with respect to size exclusion chromatography?

A. There was a huge volume of literature with respect to size exclusion chromatography by 1994.

Q. Were there texts that described the use of size exclusion chromatography?

[1410]

A. There were textbooks, there were individual book chapters, there were numerous scientific articles.

Q. And what was the state of the art with respect to size exclusion chromatography on polypeptides?

A. The state of the art was very extensive at that time, too. Polypeptides had been studied -- in fact, polypeptides were one of the first things studied by size exclusion chromatography because the manufacturers of the chromatography medium targeted those.

Q. Let's look at PTX 553 in your binder. Do you have that?

A. Yes, I do.

Q. Can you identify that document, please?

A. Yes. This is a chapter entitled "Gel Filtration" in a book called "Protein Purification, Principles, High Resolution Methods and Applications."

Q. What's the year of that book, Dr. Grant? I believe it's on the second page.

A. 1989.

Q. And this chapter from this book, is this something you relied on in rendering your opinions in this case?

A. Yes, it is.

MR. JAMES: Your Honor, we would offer into evidence Plaintiff's Trial Exhibit 553.

MR. ACKER: No objection, your Honor.

THE COURT: Admitted.

[1411]

(Plaintiff's Exhibit PTX 553 received in evidence)

Q. Now, the title of the chapter in question, Dr. Grant, is Gel Filtration. Can you remind us what gel filtration is?

A. Gel filtration is simply another word for size exclusion chromatography.

Q. In general, Dr. Grant, what does this chapter describe in terms of size exclusion chromatography?

A. Well, it describes really all aspects of the process. It describes the instrumentation, it describes the chromatographic media, it describes the type of detection that is often used, it describes the theory and practice of size exclusion chromatography and it talks about the interpretation of the results.

Q. Now, let's turn to page 70, please, in that chapter, and look at table 3-2. Could you explain for the Court what is shown in that table?

A. Table 3-2 is entitled "Characteristics of Some Media for High Resolution Gel Filtration Proteins." So what it's doing is it's just giving some specifications and description of the types of gel filtration media that was available.

Q. What is the first entry?

A. First entry is Superose 12.

Q. What type of information does this table provide about Superose 12?

A. It provides a lot of different things. It provides the [1412] identification of the material that it's made out of, it provides its effective molecular weight fractionation range, it provides such things as its pH stability, the approximate void volume fraction, and certain types of buffers that it can use to do chromatography Superose 12.

Q. Can you turn to page 72, please? And if we could look under "theoretical considerations" at the bottom of the page. Could you read the first sentence of that first paragraph into the record, please?

A. "The retention of solutes is, in ideal gel filtration, governed solely by the differences between the solute dimensions and the pore dimensions."

Q. What does that mean, Dr. Grant?

A. Let me define a few things. The first thing is solute dimensions. What that refers to is the solute is the substance that's dissolved in the liquid that's run through the column to do the procedure. So the solute dimensions referring to the size of the molecule or its hydrodynamic volume, which is a term we used before. Then pore dimensions refers to the gel itself which is doing the separation and the pores are the channels in the gel.

If you remember, we had a sponge last week which showed there were holes in the sponge and that molecules of a certain size couldn't enter, but molecules of another size could enter and those holes in the sponge are what we mean by [1413] pore dimensions and those pores have different sizes, some are larger, some are smaller. So what this is referring to is that the retention behavior of molecules really is based on the relationship of the solute size to the pore size and that's how the separation takes place.

Q. Thank you. If we look at the last sentence in that paragraph it begins with the words, "it is readily." Could you read that sentence into the record, please, Dr. Grant?

A. "It is readily seen that calibration versus molecular weight is only meaningful for solutes of similar shape."

Q. Dr. Grant, what does that suggest to you?

A. This reiterates once again what we've said many times and that's that in order for conventional size exclusion chromatography to give an accurate molecular weight, the standards that you use have to have the same size and molecular relationship as the substance being measured.

Q. Now, that relationship between size and molecular weight, is that necessary for universal calibration?

A. No, it's not. Universal calibration is a technique that's been developed to bypass that requirement, and as I said previously just a little while ago, it uses another physical principle called viscosity to compensate for the difference in size of the molecular weight relationship.

Q. Dr. Grant, could you turn to Plaintiff's Trial Exhibit 514 in your binder, please? Can you identify that document?

[1414]

A. Yes, this is another book chapter. The chapter is entitled, "Gel Permeation Chromatography," and it's found in a book called "Molar Mass Measurements in Polymer Science" by Billingham.

Q. And is this a chapter that you relied on in rendering your opinions in this case?

A. Yes, it is.

MR. JAMES: Your Honor, plaintiffs would offer into evidence Plaintiff's Trial Exhibit 514.

MR. ACKER: No objection, your Honor.

THE COURT: Admitted.

(Plaintiff's Exhibit PTX 514 received in evidence)

Q. Dr. Grant, just so we have it in the record, what is the date of this chapter from the Billingham book?

A. 1977.

Q. Now, Dr. Grant, can you tell us generally what is described in this chapter?

A. Well, similar to the chapter that we just discussed, this chapter really talks about all aspects of size exclusion chromatography from the instrumentation to the detection to the theory and practice and to the interpretation of the results.

Q. Could you turn to page 211, please? And at the bottom of the page, there's a Section 8.3.4, calibration with polymer fractions. Do you see that?

A. Yes.

[1415]

Q. Can you explain what is described, just in a general sense, in this section of this chapter?

A. In a general sense this is dealing with how you use polymer fractions, which in this case are the same as self standards, to calibrate a column.

Q. Okay, and if we look at the second paragraph, the first sentence, could you read that into the record, please?

A. "Direct calibration with the polymer under test can be achieved by using narrow distribution fractions of the polymer, prepared either by preparative fractionation or by preparative scale GPC."

Q. Dr. Grant, what does that mean?

A. First of all, GPC stands for gel permeation chromatography which is another way of saying size exclusion chromatography. And what it means is that you can prepare these self standards by some fractionation method of a standard that has a larger molecular weight distribution.

Q. So when it says narrow distribution fractions of the polymer, what are those, Dr. Grant?

A. Well, those are the self standards. The narrow distribution really refers to a distribution that is narrower than the whole polymer which you are fractionating.

Q. What are the techniques that are suggested here for creating those self standards?

A. One of the techniques is size exclusion chromatography.

[1416]

Q. Now, let's look at the -- there's a sentence I think we skip over one sentence, the sentence begins, "Where broad distributions." Do you see that?

A. Yes.

Q. Can you read that sentence into the record, please?

A. "Where broad distributions are used it is necessary to calculate M peak for each fraction, from measurements of average molar mass and some assumption about the form of the molar mass distribution."

Q. Now, Dr. Grant, let's see, the measurements of average molar mass referred to in that sentence, what are those?

A. Those are number average, weight average, that type of average molecular weight.

Q. And for your self standard, how would you obtain those?

A. You would obtain them by measuring them by some other method, some absolute method such as light scattering or osmometry.

Q. And then it says in the first part of the sentence that where broad distributions are used, it is necessary to calculate M peak for each fraction. What does that mean?

A. Well, this is the beginning of the description in this book chapter of how to do that adjustment that I demonstrated on the slide when I was standing out on the floor there. And what it means is that, if you recall, since a number average or a weight average is not going to have a tie-in associated with it [1417] that's equal to the peak, you have to do some calculation or adjustment to be able to find what the accurate molecular weight is at the peak.

Q. If you look at the last sentence, Dr. Grant, it says methods for calculating M peak have been reviewed by Dawkins, do you see that?

A. Yes I do.

Q. Do you know what the reference to Dawkins is there?

A. Yes, I've looked at that reference. Dawkins is a paper from the early 1970's, I believe, that talks about several different types of methods that had already been developed by that time to do this adjustment, this calculation of the peak molecular weight from other types of average molecular weights.

Q. Now, let's look at the next sentence and the next paragraph. It begins with, "Where the gel chromatograms for fractions." Could you read that sentence for us, Dr. Grant?

A. "Where the gel chromatograms for fractions are not fitted by a simple mathematical function a rather different approach is needed."

Q. Thank you. Can you explain what that means?

A. Yes. Well, it depends upon what the molecular weight distribution in your chromatograms is, but in many cases that distribution is quite regular and if that's the case, there is a very simple mathematical calculation can be used to convert number average or weight average molecular weights into the [1418] peak. But in other cases if the distribution is a little bit less regular there are more advanced, more detailed mathematical treatments that can be used to do the same thing.

Q. And were those mathematical treatments described in the literature?

A. Yes, they were.

Q. Let's look in the middle of that page, Mr. Int-Hout. Dr. Grant, there's a reference to calibration with whole polymer. Do you see that?

A. Yes, I do.

Q. What is that about?

A. Well, that is the other type of self standard that we were talking about. It's simply takes a polymer that was synthesized and uses it without fractionation to do the calibration of the column.

Q. Was that technique well described in the literature in 1994?

A. Yes, it was.

Q. Let's look at PTX 566 in your binder, Dr. Grant. Do you have that?

A. I have it.

Q. Can you identify that document?

A. Yes. This is another chapter from a book. In this case the book is "Modern Methods of Polymer Characterization" by Howard Barth and Jimmy Mays and the chapter is, [1419] "Characterization of Complex Polymers by Size Exclusion Chromatography in High Performance Liquid Chromatography."

Q. What is the date of that book, Dr. Grant?

A. 1991.

Q. And is this something you relied on in forming your opinions in this case?

A. Yes, it is.

MR. JAMES: Your Honor, plaintiffs would offer into evidence Plaintiff's Trial Exhibit 566.

MR. ACKER: No objection, your Honor.

MR. JONES: No objection.

THE COURT: Admitted.

(Plaintiff's Exhibit PTX 566 received in evidence)

Q. Now, Dr. Grant, what is generally described in this chapter of the Barth and Mays book?

A. Again, it covers pretty much all aspects of size exclusion chromatography. It gives a description of the process, it shows characterization of the instrumentation that's used, it talks about the theory behind average molecular weights and how to determine them with size exclusion chromatography, and a lot about how to interpret the results.

Q. Let's turn to page 37. We're at the bottom of the page, there's a section entitled "Calibration Using Poly disperse Standards of Known Molecular Weight Averages." Do you see that?

[1420]

A. Yes, I do.

Q. Dr. Grant, could you tell us what is described in that section of this chapter?

A. This section describes yet another method using what are essentially self standards, poly disperse standards of known molecular weight, which means that their molecular weight has been determined by some other process besides size exclusion chromatography. In this case, it describes a computer program that helps you determine what

the accurate molecular weight at the peak of the chromatogram will be.

Q. Now, could you read into the record the first two sentences of that paragraph, please?

A. "In this method, a polymer sample of the same type for which a calibration curve is sought is available. The sample has a broad molecular weight distribution with known molecular weight averages, say, Mn and Mw, intrinsic viscosity could be used in place of either."

Q. What does it mean that a polymer sample of the same type for which a calibration curve is sought is available?

A. Means you have self standards.

Q. The next sentence that says it has known molecular weight averages say Mn and Mw. Could you explain that?

A. Again, Mn and Mw are average molecular weights that can be determined by absolute methods. Since they do not correspond to molecular weights at the same time as the peak, this [1421] paragraph is describing a process that allows you to determine the accurate molecular weight at the peak for constructing a valid calibration curve.

Q. Could we go back to Dr. Grant's illustration of the calibration curves for a moment? Dr. Grant, after going through the literature as we just did, can you explain for us what that means in terms of calibrating a size exclusion column with self standards?

A. Yes. First of all, the literature that we've gone through is only a very small part of the literature that was available in 1994 describing these processes, but I just would like to reiterate that what this all means is that in fact there are well described and valid and effective methods to take calibration curves that may be constructed from different types of average molecular weights and resolve them into a single calibration curve, so that in fact in the end you only had single valid calibration curve, and gives you an accurate molecular weight at the peak of your measuring.

Q. Do you have an opinion about whether a person of skill in the art in 1994 could have used self standards to accurately determine the molecular weight distribution of a copolymer-1 sample?

A. Yes, I do. I'm sure that they could have, because the literature that we just discussed tells you how to do it.

Q. Do you have an opinion about whether a person of skill in [1422] the art in 1994 could have used self standards to accurately determine the percentage of copolymer-1 molecules between two kilodaltons and 20 kilodaltons or over 40 kilodaltons?

A. Yes, I do. In my opinion they could because the calibration curve allows you to do the molecular weight distribution analysis and that molecular weight distribution analysis is then used to calculate the percentage of molecules that are between any two molecular weight values.

Q. Do you have an opinion as to whether determining these molecular weight characteristics

for a copolymer-1 sample based on the teaching in the patent would have required undue or excessive experimentation as of 1994?

A. I don't think so. I think it was well laid out in the literature and it wouldn't have been that difficult to do.

Q. Mr. Int-Hout, if we could go back for a moment to Plaintiff's Trial Exhibit 566 and specifically page 36. Dr. Grant, could you remind us again what PTX 566 is?

A. Yes, it's a chapter from the book by Barth and Mays on gel permeation or size exclusion chromatography.

Q. If we look at the top half of page 36, there's a sentence that says, "There are five primary methods of determining the relationship between molecular weight and retention volume." Do you see that?

A. Yes, I do.

Q. Which of those methods have we been discussing so far this [1423] morning?

A. We've been discussing the number 3 method.

Q. Can you explain that?

A. Well, number 3 says they use poly disperse polymer standards of known molecular weight averages. Poly disperse polymer standards in this case refer to self standards, the same material as the compound that you're trying to measure the molecular weight of, and you know the molecular weights of these standards from the use of other procedures such as light scattering or osmometry.

Q. I'd like to talk about the first entry. It says, "Derivation from a universal calibration curve."

A. Yes.

Q. What does that mean?

A. That simply acknowledges that universal calibration was a procedure that was well known at the time of this writing that could be used to determine the relationship between molecular weight retention volume of the sample.

Q. Let's turn back, if we could for a moment to Plaintiff's Trial Exhibit 514 in your binder that's the Billingham chapter and page 213, please. At the top of the page, there's a section that says universal calibration procedure. Do you see that?

A. Yes, I do.

Q. Dr. Grant could you explain what's provided in this section [1424] of Plaintiff's Trial Exhibit 514?

A. This section essentially is talking about the various different derivations from different laboratories that have been presented in the literature, that underpins the basis for universal calibration. But they all end up using some property like viscosity.

Q. Could you read the first sentence of that?

A. "If well characterized" --

Q. I'm sorry, Dr. Grant. Let me make sure I'm directing you to the right sentence.

A. I'm sorry.

Q. Yes, if you could read the first sentence of the first paragraph, please.

A. "If well characterized fractions of the polymer under test are not available and the effort required to prepare them is not worthwhile, then a calibration curve can be obtained by making some assumption about the mechanism of GPC separation."

Q. What is the assumption about the mechanism of GPC separation that's referred to in that sentence?

A. I believe that the assumption that they're referring to here is that molecules of the same size come out of the column at the same time.

Q. And is that assumption described further down in that paragraph, Dr. Grant?

A. Yes, I think it is.

[1425]

Q. Where is that?

A. At the bottom there that's highlighted, it says that the product of the intrinsic viscosity, that's the eta, the Greek letter in the brackets there, times M, which is the molecular weight for any flexibly coiled molecule is directly proportional to the hydrodynamic sphere which is its size.

Q. Maybe we can try to explain this a little bit further here. First of all, the flexibly coiled molecule, what is that?

A. Well, that refers to the fact that the molecule doesn't have any particular stationary shape, that it has an overall average shape in solution.

Q. And in 1994, would a person of skill in the art have had an understanding as to the shape of copolymer-1?

A. Yes, I believe they would have.

Q. And what would that understanding have been?

A. I believe that the person skilled in the art would understand copolymer-1 to have been what we call a random coil, which is basically a flexible molecule that is basically constantly changing in solution but maintains an overall average size.

Q. And would that, the description you just gave, is that the same as a flexibly coiled molecule?

A. Yes.

Q. It says, "For universal calibration that the product," which I think means multiplying these two things together, "the [1426] product of the intrinsic viscosity and molecular weight is directly proportional to the volume." Could you help us understand that a little bit more?

A. So in this case with universal calibration you don't have to use standards that have the same size to molecular relationship as the product you're trying to measure. You can use a variety of different standards. Lots of things have been used, such as other polypeptides, dextrans, polyethylene glycol, things like that, and this size relationship is compensated for because there is a direct relationship between the product of the intrinsic viscosity and its molecular weight that can be related to size. So when that product number changes, this hydrodynamic volume of the molecule changes. Say

it the other way around, the hydrodynamic volume determines the product of those two parameters.

Q. And how does universal calibration make use of that fact or that relationship?

A. It allows you to use any number of different standards without regard to the size to molecular weight relationship because now you size to the product relationship and you simply use that information to construct a calibration curve where now instead of molecular weight on the Y axis you have intrinsic viscosity times molecular weight and that's related to retention time on the X access very similar to the way that size exclusion chromatography is calibrated.

[1427]

Q. Now, Dr. Grant, what's your basis for saying that in 1994 you would have had an expectation that copolymer-1 is flexibly coiled?

A. Well, my basis for saying that is based upon the literature that was available describing the types of conformations molecules of these types can form, copolymer-1 is a linear polymer with a rather evenly distributed charge and in my opinion that copolymer is going to have a random coil type of conformation.

Q. Let's look at the next sentence. Actually, I'd like to look at the bottom of the page, the sentence that begins with "this observation" just under the table there, Mr. Int-Hout, and it spans over on -- two pages further. Could you read the highlighted sentence, Dr. Grant?

A. "This observation first made by Benoit, I think that's how you pronounce the person's name, and his

co-workers is amply confirmed by the experiment as shown in figure 8.9 where it is seen that a wide range of homopolymers and copolymers having linear," and it says "branded" I think it meant "branched." I think That's a typo. "...linear and branched structure all fall on a common curve when intrinsic velocity times molecular weight is used as the calibrating parameter."

Q. What does that mean when it says the homopolymers and copolymers having linear and branched structures all fall on a common curve when you use this intrinsic viscosity times [1428] molecular weight calibrating parameter?

A. That means that Benoit, who was actually the originator of universal calibration, the first person to describe it, has done studies that indicates to him that it is an effective technique for a wide range of different types of polymers. Single monomeric polymers, copolymers with more than one monomer in it, linear polymers, branch polymers, so a wide range of polymers. It's an effective technique for many, many things.

Q. Let's take a look now at Plaintiff's Trial Exhibit 553. That's the Janson book chapter.

A. Okay.

Q. Could you turn to page 74.

A. Okay.

Q. Does this section of this chapter describe universal calibration -- Dr. Grant let me pull out, Mr. Int-Hout if you could pull out the first full paragraph on that page and you see in the middle of the

paragraph, Dr. Grant, a sentence that begins with the name Benoit?

A. Yes.

Q. Could you read that, please?

A. "Benoit and co-workers proposed the hydrodynamic volume as the retention decisive parameter for the solute in SEC. This approach has been shown to be applicable to a wide variety of solute shapes and solute solvent systems. Calibration of a [1429] column using hydrodynamic volume or viscosity radius has therefore been called universal calibration."

Q. You could stop there. And, Dr. Grant, could you just briefly explain what that says?

A. Very similar to what I said before. Benoit and co-workers, the originators of universal calibration, it's stated once again in this book that it's applicable to a very wide variety of polymers and it's effective for determining the molecular weight.

Q. Dr. Grant, can you -- you mentioned the Benoit articles which are cited there I think in that sentence or they were cited in the previous sentence. Do you know the date of the original Benoit articles on universal calibration?

A. I don't remember off the top of my head, I'm sorry.

Q. We can look back at 514.

A. Okay, in the references to 514 it cites the two Benoit articles and they are from 1966 and 1967.

(Continued next page)

[1430]

BY MR. JAMES:

Q. Thank you. Now, Dr. Grant, we looked at these three book chapters which were published prior to 1994. Was there more literature on the universal calibration than what we looked at today?

A. Yes, there was quite a bit more. This is just a small sampling.

Q. And do you have an opinion as to whether a person of skill in the art in 1994 could have used universal calibration to accurately determine the peak average molecular weight of a copolymer-1 sample?

A. Yes, I certainly think so.

Q. What's the basis for that opinion, Dr. Grant?

A. The basis for the opinion was the opinion of the originators of the technique and other people in the literature throughout the years who have studied a wide variety of different polymers. And I have seen nothing that suggests that co-polymer-1 wouldn't be equally as amenable to having molecular weight determined by universal calibration.

Q. And do you have an opinion about whether a person of skill in the art in 1994 could have used universal calibration to accurately determine the molecular weight distribution of a copolymer-1 sample?

A. Certainly. I mean, universal calibration is just another way to make a calibration curve. Once you have that, you can [1431] easily determine the molecular weight distribution, and from that you can

determine the number of molecules that occur between two molecular weight boundaries.

Q. Do you have an opinion as to whether a person of skill in the art in 1994 could have used universal calibration to accurately determine the percentage of copolymer-1 molecules between two kilodaltons and 20 kilodaltons or over 40 kilodaltons in a copolymer-1 sample?

A. Yes, I do. My opinion is that they could for the reasons I just stated.

Q. And, Dr. Grant, do you have an opinion about whether a person of skill in the art in 1994 could have used universal calibration to accurately determine the percentage of trifluoracetyl copolymer-1 molecules that were used in making a copolymer-1 sample?

A. Yes. It would have been done exactly the same way.

Q. When you say "exactly the same way," exactly the same way as what?

A. As universal calibration was done for copolymer-1; that is, to calibrate column with the universal calibration, determine the molecular weight distribution, and calculate the number of molecules of TFA copolymer-1 that are between any two molecular weight boundaries.

Q. Now, do you know or do you have an opinion as to whether determining these molecular weight characteristics that we just [1432] talked about for a copolymer-1 sample, based on the teaching in the patent using universal calibration would have required undue or excessive experimentation?

A. In my opinion, I don't think it would have.

Q. Why not?

A. Well, again, because by 1994 universal calibration was extensively described and performed by many scientists and many laboratories quite effectively. I think a person skill in the art could've used all that information to set up the procedure and determine the molecular weight without a great deal of additional experimentation.

Q. And but now, Dr. Grant, just so we're clear, you never used universal calibration, correct?

A. No, I haven't.

Q. And why is that?

A. I've never had the need for it in my research.

Q. And do you have an opinion as to whether the patent provides adequate disclosure for a person of skill in the art to determine whether a copolymer-1 sample meets the molecular weight limitations of the claims of the patents in suit using universal calibration?

A. I think that it does. Because patents in suit simply say using a suitably calibrated gel filtration column, and universal calibration is one way of suitably calibrating that column.

[1433]

Q. Dr. Grant, let's turn to plaintiffs' trial exhibit 26 in your binder, please.

A. Okay.

Q. Can you identify that document?

A. This is the '550 patent.

Q. Have you studied this document?

A. Yes, I have.

Q. Did you rely on this document in forming your opinions in

this case?

A. Yes, I have.

Q. Now, were you in the courtroom for Dr. Zeiger's testimony?

A. Yes.

Q. And did you hear Dr. Zeiger testify that all of the asserted claims of the patents in suit that list specified molecular weight ranges, would have been obvious to a person of ordinary skill in the art?

A. Yes, I heard -- I heard that.

Q. And that his opinion was based on the '550 patent?

A. It was based on the '550 patent, yes.

Q. Did you agree with that opinion?

A. No, I do not.

Q. Will you explain why not?

A. As far as I can tell, there is nothing in the '550 patent, and, in fact, nothing in the previous literature either, that mentions copolymer-1 that has a molecular weight anywhere close [1434] to the molecular weight described in the patents in suit.

Q. Is there anything in the prior art that suggests a lower molecular weight copolymer-1, Dr. Grant?

A. No, not to my reading.

Q. Now, did you hear Dr. Zeiger testify that the copolymer-1 disclosed in the '550 patent would have an overlap distribution with the claimed copolymer-1 compositions?

A. Yes, I did.

Q. Does the '550 patent disclose peak average molecular weight values that fall within or overlap the peak average molecular weight values of the claims of the patents in suit?

A. No, it does not.

Q. Does the '550 patent disclose anything about the molecular weight distribution of a copolymer-1 sample?

A. There's nothing in the '550 patent that talks about molecular weight distribution.

Q. Is there any indication from the '550 patent of the degree of overlap in distribution between the copolymer-1 as described in the '550 patent and the co-polymer-1 that's claimed in the patents in suit?

A. No, there isn't.

Q. Now, in terms of molecular weight of copolymer-1, Dr. Grant, what molecular weight values are suggested by the '550 patent?

A. '550 patent suggests molecular weight values for [1435] copolymer-1 between 15,000 and 25,000 daltons.

Q. Okay, let's look at column one, line 65 -- I'm sorry, line 57, that paragraph.

And, Dr. Grant, could you explain what's disclosed in that paragraph of the '550 patent please?

A. Well, this paragraph talks about a copolymer that is comprised of a synthetic water soluble that is a synthetic water soluble material with a plurality, it says a number of amino acids with a molecular weight being in excess of 10,000 and preferably above 18,000, the copolymer being characterized by a net positive electrical charge and by content of a lesser quality of a negative electrical charge.

Q. Okay. And, Dr. Grant, is that a specific disclosure of copolymer-1?

A. No, it's not.

MR. JONES: Objection, your Honor. This is outside the scope of his expertise. It's been -- and it's not mentioned in his expert reports.

MR. JAMES: It is addressed in his expert reports. He addressed the obviousness issue, your Honor, and he's also offered opinions on the meaning of copolymer-1 as your Honor has defined copolymer-1.

MR. JONES: In Prior trials, your Honor, but --

THE COURT: Pardon me?

MR. JONES: In the product claims, but not as a [1436] biochemist, your Honor.

THE COURT: You can make those arguments. Overruled.

I'll hear. Go ahead.

A. Could you repeat the question?

Q. I believe the question was, is the description in column one of the '550 patent that's highlighted, is that a specific disclosure of copolymer-1?

A. In my opinion it's not. According to the claims accepted by the Court, there's nothing in here that would lead me to believe that this is describing copolymer-1. It's just describing some copolymer.

Q. And is there any elucidation in that paragraph of the amino acids in the copolymer?

A. No, there's not.

Q. Does it describe the molar ratio of amino acids?

A. No, it does not.

Q. Let's look at column two of the '550 patent, line 19. And there is a description of a preferred copolymer, according to the present invention, that comprises alanine, glutamic acid, lysine and tyrosine, and then it describes further down that they're found in a molar ratio of six to two to 4.5 to one; do you see that?

A. Yes, I do.

Q. Is that a specific description of copolymer-1 Dr. Grant?

A. Yes, in my opinion it is, because it meets the Court's [1437] description or definition of what copolymer-1 is.

Q. Now, why is that, why does it meet the Court's definition of copolymer-1?

A. Because it lists the same four amino acids that are in copolymer-1, and it lists the same average,

molar ratios of those amino acids that are found in copolymer-1.

Q. And what's the molecular weight range stated for copolymer-1 in this passage?

A. 20,000 to 25,000 daltons.

Q. Let's look at claim one of the '550 patent, please. And, Dr. Grant, there is a, under subheading one it says that the mixture consists of essentially of alanine, glutamic acid and lysine and tyrosine, and it gives a molar ratio of six to two to 4.5 to one; do you see that?

A. Yes, I do.

Q. Is that a specific description of copolymer-1?

A. Yes, it is.

Q. And what's the molecular weight stated in claim one?

A. 15,000 up to 25,000 daltons.

Q. Now, in your opinion, Dr. Grant, would these disclosures of copolymer-1 have suggested to a person of ordinary skill in the art copolymer-1 having a molecular weight limitations claimed in the patents in suit?

A. No. In my opinion, I don't see how they would suggest copolymer-1 would have the limitations claimed in the patents [1438] in suit.

Q. What type of average molecular weight is disclosed in the '550 patent?

A. It's not clear. You really can't tell what type is disclosed.

Q. Does the patent say?

A. No, it doesn't.

Q. Now, does the '550 patent suggest to a person of skill in the art copolymer-1 having a molecular weight limitation of the claims of the patents in suit?

A. I don't think so, no.

Q. In terms of molecular weight, what does the '550 patent suggest to a person of skill in the art?

A. The '550 patent suggests that copolymer-1 would have molecular weights of between 15,000 and 25,000 daltons.

Q. Now, what does the '550 patent disclose with respect to the molecular weight distribution of copolymer-1?

A. It doesn't say anything about the molecular weight distribution of copolymer-1.

Q. And you heard Dr. Zeiger testify that the copolymer-1 described in the '550 patent would be expected to be polydisperse, right?

A. Yes.

Q. What does that mean, what does polydisperse mean?

A. Polydisperse is just a word to indicate that there is, [1439] there are components of more than one molecular weight.

Q. And would knowing that a sample is polydisperse tell you anything about the molecular weight distribution of that sample?

A. No. Samples of any molecular weight distribution are polydisperse.

Q. And, Dr. Grant, I asked you a question a moment ago about whether the '550 patent discloses any molecular weight distribution?

A. Yes.

Q. Could you explain again for us what a molecular weight distribution is?

A. Okay. So in the mixture of polypeptides where each of the molecules have a different molecular weight, the distribution is identified by the r ge of that molecular weight. So let's say, for instance, if there is a distribution of molecular weight between 2,000 and 20,000 daltons, the description of that distribution is the polydispersity. It's the molecular weight distribution that applies to that sample. Is that --

Q. Does the '550 patent disclose that?

A. No. It doesn't say anything about that at all.

Q. Does it provide any, provide you with any information from which you could calculate it?

A. No, it doesn't.

Q. Now the '550 patent cites to the Teitelbaum 1971 article, [1440] correct?

A. Yes, it does.

Q. And could you look at plaintiff's trial Exhibit 499 for a moment?

A. Okay, I have it.

Q. Now, can you identify plaintiff's trial exhibit 449?

A. Yes. This is the Teitelbaum article, which is the first article I believe that describes the synthesis of copolymer-1.

Q. And could you look at table one, please? It's found on the 2nd page, page 243?

A. Okay.

Q. Table one discloses molecular weights for two batches of copolymer-1, right?

A. That's correct.

Q. And the molecular weights, where are they found on table one?

A. They're found at the bottom right-hand corner of the table across from the column heading -- row heading, excuse me, molecular weight.

Q. And does the reference say what type of average molecular weight is described there?

A. No, it doesn't.

Q. Does the Teitelbaum article describe how the molecular weights were obtained?

A. It describes the use of an ultracentrifugation.

[1441]

Q. Does the Teitelbaum reference disclose a molecular weight distribution for copolymer-1?

A. No, it doesn't.

Q. Does it disclose information from which you could calculate a molecular weight distribution?

A. No, it doesn't.

Q. Does it disclose what the polydispersity of copolymer-1 was?

A. No, it does not.

Q. Now, does the synthetic scheme that's described in the '550 patent or in Teitelbaum, did that -- does that scheme alone given you enough information from which you can determine the molecular weight distribution for a copolymer-1 sample?

A. No, it doesn't.

Q. And with respect to copolymer-1 fractions, the percentage of molecules having any particular molecular weight, what information does the '550 patent or Teitelbaum 1971 – what information do they provide?

A. They don't provide any information that would allow you to calculate that or determine that.

Q. And does the 19 let -- strike that.

Does the '550 patent or the Teitelbaum reference that it cites, contain any disclosure of the molecular weight distribution for a TFA copolymer-1 molecule?

A. No.

[1442]

Q. Could you turn in your binder to plaintiffs's trial exhibit 509, please?

A. Okay.

MR. JAMES: And we'd like to put up on the screen the second page, the abstract in the lower right-hand

corner. And we'll need to also pull in the remainder of the abstract from the next page.

Q. Dr. Grant, can you identify plaintiff's trial exhibit 509, please?

A. Yes. This is a -- I believe it's an abstract that was published with the authors Dvora, Teitelbaum, Cynthia Web, Ruth Arnon and Michael Sela, in the Israel Journal of Medical Science in 1974.

Q. And does that abstract discuss copolymer-1?

A. Yes, it does.

Q. And if we could look at the sentence that begins toward the bottom of the 1st page of the abstract, it begins with molecules; you see that?

A. I do.

Q. Could you read that into the record, please?

A. Molecules of identical composition, but not -- but of molecular weight either lower than 17,000 or higher than 50,000, proved ineffective.

Q. Now, Dr. Grant, what does that suggest to you with respect to the activity of copolymer-1?

[1443]

A. That suggests to me that the activity of copolymer-1 is found in molecules that have a molecular weight higher than 17,000.

Q. And what does it tell you about the copolymer-1 that's of a molecular weight as claimed in the patents in suit?

A. It tells me that they're talking about molecular weight that's significantly higher than the molecular weight claimed in the patent in suit.

Q. And how would this -- how does this abstract impact your opinion as to whether the art, the prior art as a whole would have motivated a person of skill in the art to make copolymer-1 having the characteristics claimed in the patents in suit?

MR. JONES: Again, your Honor, this is new opinion. There is no discussion of this reference being used in regard to teaching way or any other part of the obviousness – excuse me.

MR. JAMES: He did discuss this in terms of the obviousness case, your Honor.

MR. JONES: No in terms of teaching, your Honor.

THE COURT: Overruled. Go ahead.

A. Would you repeat the question, please?

Q. Yes. Let me ask a different question first.

What does the abstract suggest with respect to the activity of copolymer-1 having molecular weight less than 17,000?

[1444]

A. The abstract says that copolymer-1 was ineffective, which suggests that it had no activity.

Q. And how would this impact the person of skill in the art with respect to being motivated to make a low molecular weight copolymer-1 sample?

A. A person skilled in the art would look at this article and see that something below 17,000 had no activity.

I see no reason why a person skilled in the art would want to make anything below 17,000.

Q. Dr. Grant, did you hear Dr. Zeiger testify about the EP-620 publication?

A. Yes, I did.

Q. Can you turn in your binder to defendant's trial exhibit 1970, please?

A. Okay.

Q. Is that the 620 EP publication?

A. Yes, it is.

Q. And have you reviewed this document?

A. I have.

Q. Are you familiar with the Court's construction of the term "copolymer-1?"

A. Yes, I am.

Q. And do you have an understanding as to what the Court's construction of copolymer-1 suggests with respect to how copolymer-1 is made?

[1445]

A. Yes. The Court's construction suggests that copolymer-1 is made by a chemical synthesis method that involves joining amino acids that are present as N-carboxyanhydride derivatives.

Q. Now, are the copolymers that are described in the '620 patent, are they made according to an Ncarboxynhydride process?

A. No, they are not. They're made by a biological process that does not involve N-carboxyanhydride.

Q. Could you describe briefly the process cells that's set forth in the '620 publication?

A. Well, this is a recombinant DNA process. What the authors of this patent application did was to make DNA of a certain sequence of four different amino acids, same amino acids found in copolymer-1, but not of a nearly random sequence. They did it in a block synthesis type of method.

They then introduced this DNA into bacteria, and the bacteria produced protein from the DNA and – polypeptides excuse me, not -- polypeptides from the DNA. And those polypeptides had the block sequence that was programmed into the DNA. But each bacteria would only produce a single, a molecule that would produce a number of molecules, all of the molecules would have the same molecular weight and same sequence.

Q. Would each of those polypeptides that was coded by those constructs, would they have an average molecular weight?

A. No, they wouldn't. They would have a precise accurate [1446] molecular weight, because they are a well defined sequence and a well defined length, and you could determine the molecular weight simply by adding up the molecular weight of the atoms that they're composed of.

Q. Okay, let's look at page three.

Before we look at the specific sentence, Dr. Grant, does the EP-620 publication describe any copolymer-1 compositions as the Court has construed the term copolymer-1?

A. I don't think that it does.

Q. Why not?

A. Because the Court has construed copolymer-1 to be a complex mixture of polypeptides of different lengths and different sequences.

And what this publication describes are single molecules modeled after copolymer-1, but that aren't in fact copolymer-1, according to the Court's description.

Q. Dr. Grant --

MR. JAMES: Perhaps we should just put up the Court's construction of copolymer-1. Do you have that available?

Q. Is this the construction of copolymer-1 as found in the Court's order?

A. Yes.

Q. And could you explain your opinion as to why the '620 patent does not disclose copolymer-1 as, excuse me, the '620 publication does not disclose copolymer-1 as defined here?

[1447]

A. Okay, yes. First of all, this definition talks about a mixture of polypeptides, and the '620 publication does not describe making the mixture of polypeptides. They are composed of alanine, glutamic acid, lysine and tyrosine. But I don't think

even the molar ratios that are shown in this publication are 6:2:5:1.

And certainly the Court's description says that the product of copolymer-1 is non-uniform with respect to molecular weight in sequence. And the products that are made by the '620 publication are uniform with respect to molecular weight and sequence, and they are not synthesized by polymerization of suitably protected amino acid N-carboxyanhydride.

So just about everything about the Court's description is ppposite what this publication describes.

Q. Let's look at page three, lines 14 to 16. You see a sentence there -- and we're back in the EP-620, yes. Do you see a sentence there that begins, more specifically?

A. Yes.

Q. Could you just read that sentence into the record, please?

A. "More specifically, a preferred copolymer may consist of alanine, lysine, glutamic acid and tyrosine, and have a molecular weight between about 5,000 and 50,000 daltons. Further, the method of the subject invention can also be used to make fusion proteins."

Q. Now the reference to 5,000 and 50,000 daltons, are those [1448] references to average molecular weights?

A. No, they're not.

Q. Is that a range of molecular weights that's stated there of average molecular weights?

A. It says between 5,000 and 50,000 daltons. It is a range, but it's not a range of average molecular weights. It's a range of specific molecular weights.

Q. And how do you know that?

A. I know that because of the process that the publication describes for producing the copolymer.

Q. Is there any disclosure in the '620 EP publication of measuring molecular weights by size exclusion chromotography?

A. No, there's not.

Q. Is there any disclosure in the '620 EP publication of peak average molecular weight for a copolymer-1 sample?

A. No.

Q. Is there any disclosure in the '620 EP publication of a molecular weight distribution for a copolymer-1?

A. No.

Q. Let's look at page five, lines 28 to 33. And I'd like to focus on the paragraph entitled "size selection of ligation products."

Maybe before we read the sentence in question, can you explain generally what size selection of ligation products means?

[1449]

A. Yeah. The ligation products simply refers to the product of the bacteria that's making, in this case a single uniformed copolymer. And it describes the

fact that they want to select certain sizes that are being made, molecular weight sizes.

Q. And could you read the sentence that begins, "products are detected?"

A. "Products are detected by staining with ethidium bromide in the region corresponding to the desired size range, 400 to 600 nucleotides is excised. Synthetic genes of 400 to 600 nucleotides encodes polypeptides of 15,000 to 23,000 daltons.

Q. Now, does that indicate the size of the polypeptides that the authors were interested in, Dr. Grant?

A. Yes, it does.

Q. What was that size?

A. 15,000 or -- between 15,000 and 23,000 daltons.

Q. And is there a suggestion in this patent to make a copolymer-1 having average molecular weight lower than that number?

A. No, there is not.

Q. Dr. Grant, are you aware of any commercial product ever having been marketed that arose from the technology that's disclosed in the '620 EP publication?

A. No, I'm not.

Q. Now, Dr. Grant, I'd like to turn now to the testimony of Dr. Scandella in which he talked about Teva's molecular weight [1450] development history. I'd like to do that very briefly.

A. Okay.

Q. Now, do you agree with Dr. Scandella that it took Teva several years to come up with a method to accurately measure the molecular weight of copolymer-1?

A. No, I don't.

Q. Why not?

A. Well, because my reading of the documents that have been supplied to me show, I think quite clearly, that as early as 1987, Teva was using copolymer self standards to determine the molecular weight, and they were doing it effectively and used that procedure for many years thereafter.

Q. Now, Dr. Grant, let's turn briefly to DTX-3275.

A. Okay.

Q. Can you explain to the Court what DTX-3275 is?

A. I believe it's a document from Teva that describes the determination of the relative retention time and estimation of the molecular weight distribution. It's a method history file.

Q. All right. And let's look at the page 304991, please.

A. Okay.

MR. JAMES: And, your Honor, this document is already in evidence.

THE COURT: Thank you.

Q. Now, Dr. Grant, beginning on page 304991, and continuing through 5000, what's described in this document?

[1451]

A. What is the last number?

Q. 5000.

A. Well, this document describes several different things. First of all, it describes the use of a protein standard kit that was sold by Pharmacia to do a column suitability test columns that they were using.

Q. What's a column suitability test?

A. Column suitability test is a measure of the integrity of the column; in other words, if you're going to use the same column and run samples through it repeatedly, you want to make sure that the column doesn't deteriorate. And you develop some sort of test that you can apply from time to time to assess whether or not the column is still functioning appropriately and accurately.

Q. Is this a molecular weight determination when you do the column function or column suitability test?

A. No, it's not.

Q. And so why do you do it; why do you do this?

A. You do it to eliminate, to make sure the column is still functioning properly. Once you've made that determination, then you can go ahead and do your calibration and determining your molecular weight by using other standards.

Q. And what's the date of this method that we've been looking at?

A. August 3rd, 1987.

[1452]

Q. And does this document describe the use of copolymer-1 self standards?

A. Yes, it does.

Q. And does the document describe how they were measuring the molecular weight of copolymer-1 self standards?

A. Yes. It says they were using -- it's termed viscosimetry, but that's viscosity measurements.

Q. Where is that shown in this document that they were using copolymer-1 self standards measured by viscometry?

A. Well, the self standards that are used themselves are showing on the page that's 305000, and then on previous page 304999 shows the calibration curve which was made from using those self standards.

Q. Now, with respect to the molecular weight calibration using the protein standards that's referred to on page 304993, Dr. Grant, have you seen any evidence that, in fact Teva never considered this to be a molecular weight calibration or molecular weight determination method?

A. Yes, I believe it's stated as such in one of these documents.

Q. Let's look at defendant's trial Exhibit 3510. I'd like to look at the first page toward the bottom, there's some underlined text, and just that portion of the paragraph from there to the end. Could you read the underlined text into the record, Dr. Grant?

[1453]

A. The linear correlation between the Kav elution of copolymer-1 and the log molecular weight determined by viscosity was established using several columns.

Q. Okay. And what does that mean?

A. That means that they weren't limiting themselves to just one column to determine the molecular weight. They were using several other columns. And they were using a procedure that involved the calculation of a promoter called Kav.

Q. So I'm asking you about the linear correlation, between the Kav elution of copolymer-1 and the log molecular weight determined by viscosity, what is that?

A. That's construction of a calibration curve.

Q. And is that, have we seen that calibration curve that's being described there?

A. Yes.

Q. And where was that?

A. That was in the previous document.

Q. So that was in August 1987 they had this calibration curve?

A. That's correct.

Q. And what does it say in the next sentence?

A. It says "globular markers were also injected to control the column performance."

Q. What does that mean?

A. I believe the globular markers are referring to the protein kit that they purchased or from Pharmacia, and it says that [1454] they were being used as a column suitability test. That's what the column performance reference is about.

Q. We discussed that a moment ago?

A. Yes, we did.

Q. Let's look at the next page at the top. I'd like to focus on the sentence that begins "therefore?"

A. Okay.

Q. Could you read that, please?

A. "Therefore, to assure the correct function of the columns, a function test, erroneously called column calibration instead of system suitability test of column performance, using protein markers was introduced."

Q. And what does that suggest to you, Dr. Grant?

A. That suggests quite clearly to me that the globular proteins were used as a system suitability function test for the performance of the column and not to determine molecular weight.

Q. Did you see any evidence that Teva ever considered protein standards to provide accurate molecular weights for copolymer-1?

A. No, I haven't.

Q. Now, if we could, let's put up Dr. Scandella's slide number 12.

Dr. Grant, could you explain briefly what's shown on this slide?

[1455]

A. Well, this slide, as it's entitled, is different methods yield different molecular weights for the same sample.

And, if chosen, batch 13, which is the one of the samples of copolymer-1. And the red arrows indicate the different types of procedures that were used to supposedly determine the molecular weights that are shown on the boxes on the right-hand side labeled cop-1, batch 13, molecular weights.

Q. Okay, let's talk about the top arrow. Could you explain what's shown there?

A. What that says is that protein standards were used besides glatiramer chromotography, and that the molecular weight range that was determined was 42,000 to 56,000 daltons.

Q. And did you see any evidence that Teva believed that those protein standard molecular weights were accurate?

A. No, I haven't seen any evidence. In fact, I think that they've stated that they knew they weren't accurate.

Q. Now, let's -- I'd like to talk about the next two arrows, but let's turn to defendants' trial exhibit 1269 for a moment. You recognize this document, Dr. Grant?

A. Yes, I do.

Q. What is this?

A. It's a report from W.R. Grace and Company that was sent to Teva.

Q. Let's look at page 3017862, and I'd like to look at the first sentence in the second paragraph.

[1456]

Dr. Grant, could you read that sentence into the record, please?

A. "We are continuing to develop analytical techniques which may be used to identify and potentially to quantify active, inactive and toxic cop-1 batches."

Q. And what does that tell you about what Grace's task was here, Dr. Grant?

A. That tells me that Grace's task was to look at other analytical techniques that were available at the time and use them for the purpose of distinguishing whether or not particular batch of cop-1 was active or toxic.

Q. Let's look at page 3017866, briefly. That page there's something called 2D SCX SEC; you see that?

A. Yes.

Q. What is that?

A. That's a description of the method that's shown in the following paragraph. And what it means is -- first of all, SCX refers to ion exchange, which is another type of separation method. And SEC, of course, refers to size exclusion chromotography.

What the 2D means is that one was run in succession after the other; in this case ion exchange was run first and then fractions from that column were taken and analyzed by size exclusion chromotography.

Q. Okay. The very complicated figure there, at the bottom of [1457] that section, could you explain what's shown in the thing that looks like a chromatogram there at the top, the graph?

A. Yes. If you notice that's labeled SCX. That's referring to the ion exchange so that is a chromatogram, but it's a chromatogram from an ion exchange column where the separation is based upon charge.

Q. Okay. And then what are the little lines that come out from that?

A. The lines indicate that at certain times along the elution profile, the time axis, X axis there, fractions were taken or samples were taken, and then those samples were applied to individual or to size exclusion chromotography column at different times.

Q. And the molecular weight was measured for each of those fractions?

A. The molecular weight of each of those fraction was measured and is listed numerically at the bottom of the figure.

Q. And does it indicate what kind of standards were used?

A. Yes. It says that polyethylene glycol standards were used.

Q. And would a person of skill in 1994 believe that polyethylene glycol standards would give you accurate molecular weights for copolymer-1?

A. No, they wouldn't. They would have known that the size to molecular weight ratio is not the same as copolymer-1.

Q. Now, does this disclose -- let me strike that.

[1458]

I think one thing we haven't talked about yet are numbers at the bottom, 800 to 8600 or up to 11,000; what are those?

A. Those are simply the molecular weights that we determined with size exclusion chromotography of the various fractions that were taken from the ion exchange column.

Q. So those are not peak molecular weights of batches of copolymer-1, correct?

A. No, they are not.

Q. And does this 2D SCX SEC data, do these data indicate the that Teva was struggling to determine the molecular weight of copolymer-1?

A. Not in my opinion. This data has nothing to do with the determining the molecular weight of copolymer-1.

Q. All right, let's look at 3017872. There is a section there entitled vapor phase osmometry, studies of molecular weight; you see that?

A. Yes, I do.

Q. What is vapor phase osmometry?

A. Vapor phase osmometry is one of the two types of osmometry techniques that could be used to determine the molecular weight of a sample.

Q. And let's look in the third paragraph, the sentence that begins with the results.

Dr. Grant, could you read those, those two sentences?

[1459]

A. "The results, after base line correction, yields Mn equals 638 daltons, an order of magnitude lower than the expected value of Mn equals 7,000 reported by Teva for this cop-1 batch."

Q. Could you read the next sentence as well?

A. "The reason for this discrepancy appears to be the disassociation of cop-1 under these conditions which leads to an artificially low number average molecular weight."

Q. Now, does this indicate that Grace believed these were accurate molecular weights?

A. No. They say they think it was artificially low.

Q. Does this indicate that Teva was struggling to determine the molecular weight of copolymer-1?

A. No.

Q. Let's go back now to Dr. Scandella's slide 12, please.

So the next two arrows are entitled SEC Peg standards and osmometry. Could you explain the data that's shown there, Dr. Grant?

A. Yes. The data that's shown there, the 800 to 11,000 daltons for the SEC PEG standards comes from that 2D analysis that we just finished talking about where they did ion exchange followed by size

exclusion chromatography. And this was not a determination of the average molecular weight of a copolymer-1 batch.

In essence, what it is is analysis of the molecular [1460] weight distribution. But since it's using PEG standards, which are not appropriate standards for determining molecular weight of copolymer-1, there's no way to tell if these values are accurate or not.

Q. Is there any indication in the memo that Grace believed those were accurate molecular weights for copolymer-1?

A. Not that I was able to see.

Q. And is there any indication that Teva or Grace believed that the osmometry or SEC PEG standard data shown in this slide, slide 12, that they believed those data were accurate molecular weights for copolymer-1?

A. I haven't seen any indication to that end; in fact, the opposite is true.

Q. Let's look at defendant's trial exhibit 1762. You recognize that document, Dr. Grant?

A. Yes, I do.

Q. What is this?

A. This is, again, is another memo from W.R. Grace to someone at Teva, and it reports results of preliminary screening of two batches of cop-1, batch 13 and batch 11A.

Q. Let's look at the first sentence under the summary. It's on page 3017832, John. Okay, that's good.

And, Dr. Grant, could you just read the first sentence, please?

A. "This report summarizes our results regarding the [1461] preliminary characterization of two preparations of cop-1, batches 13 and 11A. Batch 13 is highly active, 84 percent, and batch 11A has low activity, 25 percent."

Q. Does this report provide any molecular weight data for those two batches of copolymer-1?

A. Yes, it does. That's on page 3017837.

Q. Yes, that's correct. Could you look at table three, please, John. Thank you.

Now, could you explain what's shown on table three Dr. Grant?

A. Well, over on the left-hand side is the -- are the two batches of cop-1, 13, 11A. The next column shows the biological activity that was determined for both of them. And then the last column, the rather wide column, shows molecular weight. And the molecular weight determined by the viscosity, which I believe is the appropriate molecular weight for these batches, is listed as 7,000 and 11,000.

Q. Now, if you used Dr. Zeiger's definition of overlap of distributions, Dr. Grant, would there be overlap in the distribution of these two batches?

A. According to what he said, I believe that this would indicate that there would be considerable overlap in the molecular weight distribution of these two batches, yes.

Q. And what is this data, what do these data suggest about the difference in activity in these two batches that have [1462] overlapping distributions?

A. Well, it says that the activity is quite different. It's, even though there is going to be significant overlap, the function or the activity of these two batches is far from being the same.

Q. Now let's look at page 3017835, please. I'd like to look at the paragraph at the top of the page, please.

You see in the middle of the page, a sentence that begins, second?

A. Yes.

Q. And here Grace says, "Second, appropriate molecular weight standards have not yet been found." Do you see that?

A. Yes, I do.

Q. Now, from your review of the documents, Dr. Grant, does that indicate that Teva had not been able to find appropriate calibration standards for copolymer-1?

A. No, it doesn't.

Q. And in your review of the documents, what does it suggest in that regard?

A. My review of the documents suggest that Teva found that self standards of cop-1 were effective in determining accurate molecular weights as early as 1987, and that they used them for many years after that.

Q. Do you know what type of molecular weight calibration standards Teva was using when it filed its NDA?

[1463]

A. Yes. It was using the cop-1 self standards.

Q. And do you know whether Teva received approval for Copaxone using those standards?

A. Yes, they did.

Q. Did you see any evidence, Dr. Grant, that Teva struggled to develop a method to accurately determine the molecular weight of copolymer-1?

A. No.

MR. JAMES: Your Honor, I have a short amount to go, but I am at a convenient stopping point.

THE COURT: How long, approximately?

MR. JAMES: 15 minutes.

THE COURT: Okay, why don't we finish then.

MR. JAMES: Okay.

THE COURT: That would be great.

Q. Now, Dr. Grant, were you in the courtroom when Dr. Walter Owens of Mylan testified that Mylan has obtained molecular weight data using universal calibration?

A. Yes.

Q. And did you receive data from Mylan from that universal calibration analysis?

A. Yes, I did.

Q. In what form did you receive the data?

A. It was sent on CD.

Q. And when did you receive them?

[1464]

A. I think I got it Thursday night.

Q. And?

A. Last Thursday night.

Q. And have you performed an analysis of the molecular weight characteristics of Mylan's product based on the universal calibration data?

A. Yes, I did.

Q. And what did you do in terms of that analysis, Dr. Grant, over the weekend?

A. As I said, I received the data Thursday night, and then over the weekend I was able to get together by webex conference with Dr. Paul Winter, who assisted me previously. And I instructed him to take this data, and put it into an excel spread sheet like he did the first time. And I instructed him as to calculations to perform on the data so that we could get determination of the mole fractions of the samples.

Q. Now, earlier in the trial you had testified about your analysis as to whether Mylan's product meets the copolymer-1 molar fraction limitations, correct?

A. Yes.

Q. And did the Mylan universal calibration data that you were provided, did it allow you to calculate the molar fraction data for copolymer-1 molecules?

A. Yes, it did.

Q. And let's put up the molar fraction limitations slide.

[1465]

Dr. Grant, we have a slide six, it's entitled copolymer-1 molar fraction limitations. Do you see that?

A. Yes, I do.

Q. And could you explain to the Court again, very briefly, what's shown on this slide?

A. Yes. This slide shows in the gray boxes the four different molar fraction limitations that are found in the patents in suit, and under each box it lists the claims and in which patent each of those limitations is found.

Q. And were you able to calculate the percentage of molecules on a molar fraction basis for Mylan's product that are relevant to each of these claim limitation?

A. Yes, I was.

Q. And that's based on the universal calibration data?

A. It is.

Q. Let's look at the next slide. Could we have the slide with the data? I'm sorry.

Now, Dr. Grant, did you -- you can take that down.

Were you able to calculate the percentage of molecules between two and 20 kilodaltons in Mylan's product based on their universal calibration data?

A. Yes, I was.

Q. And what was the percentage between two and 20 on a molar fraction basis?

A. In all cases, it was in excess of 90 percent.

[1466]

Q. And were you able to calculate the percentage on a molar fraction basis of the TFA copolymer-1 molar fraction?

A. Yes.

Q. And what were the results there?

A. Again, the mole fraction between two and 20 kilodaltons was greater than 90 percent.

Q. And that was for the TFA copolymer-1 molar fraction?

A. Correct.

Q. And with respect to the claim limitation, Dr. Grant, for the molar fractions and for the TFA copolymer-1 molar fraction, what did you conclude, based on your review of the data that Mylan provided from universal calibration?

A. I also calculated the amount that was present over 40 kilodaltons, and found that was all below two and a half percent.

So based upon these calculations, I concluded that Mylan's product was molecular, whose molecular – was determined by universal calibration, met all of the claims of the patents in suit.

Q. And I apologize, I will --

MS. BLOODWORTH: Objection. Your Honor, are we going to receive any written documentation of these conclusions by Dr. Grant that he's testifying here to today?

MR. JAMES: I think we have produced the excel files, your Honor. Of course this was over done over the weekend so [1467] we've just produced the excel files.

MS. BLOODWORTH: I haven't seen any data moved into evidence here, and I don't have any slides with his opinions as to the results of those excel files.

MR. JAMES: Actually, I think there was evidence, because he gave his testimony about what his calculations showed, and we've produced the excel files to them.

MS. BLOODWORTH: The excel spread sheets are voluminous, and I think that was why last time when Dr. Grant testified he provided a slide that --

THE COURT: What would the slide show?

MS. BLOODWORTH: The slide would show the percentages that he's representing are greater than 75 percent the actual values, with the new method versus the old method.

MR. JAMES: That's correct, your Honor, that's what the slide would show, but that's what he testified to and they have the data from which they could cross-examine him on that.

MS. BLOODWORTH: I guess we're going to break for lunch, so.

THE COURT: Okay.

Q. Okay. Now, Dr. Grant, based on the data you have reviewed regarding the Mylan product, do you have an opinion as to whether if Mylan were to use the process described in their ANDA to make copolymer-1, the resulting copolymer-1 would satisfy the molecular weight limitations of the asserted claims [1468] of the patents in suit?

A. Yes. In my opinion, if Mylan used the process outlined in their ANDA, the substance that would be produced would be -- would satisfy all the claims of the patents in suit.

Q. Now, Dr. Grant, have you done an analysis of whether Copaxone meets the molecular weight limitations of the claims of the patents in suit?

A. Yes, I have.

Q. Have you seen any certificates of analysis for Copaxone?

A. Yes.

Q. Let's look at plaintiff's trial Exhibit 105. Dr. Grant, could you identify that document, please?

A. This is a certificate of analysis for Teva's Copaxone.

Q. And does this the certificate of analysis provide a specification with respect to molecular weight?

A. Yes. This specification reads 5,000 to 9,000 daltons.

Q. Pull up the second page, 291798, and the row, the first row under specifications there.

Dr. Grant, is that the specification that you were referring to?

A. Yes, it is.

Q. And for this particular batch of copolymer-1, Dr. Grant, what is the peak average molecular weight? A. It's 6,800.

Q. And did you rely on this document in forming your opinions [1469] in this case?

A. Yes, I did.

MR. JAMES: Your Honor, we would offer into evidence plaintiffs' trial Exhibit 105.

MR. DOYLE: We have no objection, your Honor.

THE COURT: All right, admitted.

(Plaintiff's Exhibit 105 received in evidence)

Q. Have you reviewed any data from Sandoz with respect to the molecular weight characteristics of Copaxone?

A. Yes, I have.

Q. And where were those data found?

A. Those data were found on data that were provided to us on an iron key secure -- flash drive. Excuse me.

Q. Those were electronic data?

A. Yes.

Q. Were there any data provided to you about Copaxone in the ANDA?

A. Oh, yes. There is also data in the ANDA.

Q. Let's look at plaintiff's trial Exhibit 349.

MR. JAMES: Your Honor, this is in evidence already.

THE COURT: All right.

Q. Dr. Grant, I don't know if you have the redacted version in your binder, but can you identify the document?

A. I have the redacted version.

This is a portion of Sandoz ANDA. I believe it's a [1470] later version of it.

Q. Okay. And I'll direct you to SDZ00017948.

A. Okay.

Q. Do you recognize that?

A. Yes, I do.

Q. Is this a section of the Sandoz ANDA that you reviewed?

A. Yes, it is.

Q. Let's look at the next page, and in particular at table 21.

Dr. Grant, what data does table 21 provide with respect to Copaxone?

A. Table 21 provides a range of average peak molecular weights for 27 lots of the extracted reference listed drug, which is Copaxone.

Q. And what type of molecular weight is reported there for Copaxone?

A. That's peak average molecular weight.

Q. What is the range of molecular weights provided by Sandoz there for Copaxone?

A. The range is 6,118 to 7,622.

Q. Let's look below that at table 22. Does that table provide any information about the average molecular weight of Copaxone?

A. Yes. It again provides a range of molecular weights for 28 lots of the reference listed drug.

Q. And what is the range of average molecular weights provided there for Copaxone?

[1471]

A. 5,943 to 7,495.

Q. Let's put up the slide of the average molecular weights, please.

Dr. Grant, could you explain this slide, very briefly?

A. This slide again is just a listing of the claims in the patents in suit. They're for average molecular weight, there are three of them, and they are listed in the gray position boxes; about 59 kilodaltons, about four to about nine kilodaltons, and 6.25 to 84 -- 8.4 kilodaltons, and then below each box is listed the claim number and the patent that it's found in.

Q. Okay. And now based on the data that you have reviewed, Dr. Grant, do you have an opinion as to whether Copaxone meets the average molecular weight limitation of the claims of the patents in suit?

A. Yes. In my opinion, Copaxone does meet the average weight average molecular weight limitations in the patents in suit.

Q. Put up the next slide. Let's stop there.

Now, with respect to the molar fraction limitations, Dr. Grant, did Sandoz provide you with data that allowed you to calculate the molar fraction values for Copaxone?

A. Yes, they did.

Q. And in what form was that data provided?

A. That was on that secure flash drive that I mentioned earlier.

[1472]

Q. And what did you do with those data, Dr. Grant?

A. Again, along with Dr. Paul Winter, we extracted data and poured it into an excel spread, and I instructed him how to do the calculations to come up with the answers, but the results of those calculations, which are listed on this slide for five lots of Copaxone.

(Continued on next page)

[1473]

Q. So for these five lots of Copaxone, could you explain what exactly the data are that are provided in these two columns on slide 11 shown on the screen, Dr. Grant?

A. Yes. The first column is the percent molar fraction between 2 and 20 kilodaltons, and in all cases that percent is greater than or equal to 75 percent.

Q. And in fact, the numbers are quite a bit larger than that?

A. In fact the numbers are quite a bit larger than 75 percent.

Q. And did you do an analysis of the percentage over 40 kilodaltons?

A. Yes, that's listed in the next column. Again, in all cases the percent molar fraction of above 40 kilodaltons is very low, significantly less than 2-1/2 percent.

Q. Do you have an opinion as to whether Copaxone meets the molar fraction claim limitations of the claims of the patents in suit, Dr. Grant?

A. Yes, in my opinion Copaxone does meet those molar fraction limitations.

Q. Let's go through those very briefly. The percentage of copolymer-1 molecules having a molecular weight between 2 and 20. Have you determined whether over 75 percent of such molecules are present in Copaxone?

A. Yes, I determined that. In all cases over 75 percent is present in Copaxone.

Q. With respect to the limitation, if we could look at the [1474] next part of the slide Mr. Int-Hout, of less than 2.5 percent of the molecules having a molecular weight of over 40 kilodaltons did you make a determination as to whether Copaxone meets that limitation?

A. Yes, all the batches of Copaxone meet that limitation.

Q. The next limitation is that, requires that both over 75 percent of the molecules that have a molecular weight between 2 and 20 kilodaltons and

that less than 2.5 percent of the molecules have a molecular weight over 40 kilodaltons, did you make a determination with respect to Copaxone and that limitation?

A. Yes, I did. All the batches of Copaxone meet that limitation.

Q. And the last limitation is similar except it requires that less than 5 percent of the molecules have a molecular weight over 40 kilodaltons. Did you make a determination whether Copaxone meets that limitation?

A. Yes, all the batches of Copaxone meet that limitation also.

Q. And finally, Dr. Grant, let's look at the next, we have the TFA copolymer-1 limitations. Dr. Grant, this slide shows the TFA copolymer-1 limitations of the claims of the patents in suit?

A. Yes, that's correct.

Q. Were you able to do a determination based on the data that Sandoz provided you as to whether Copaxone meets those [1475] limitations?

A. Yes, I was.

Q. What did you conclude?

A. I concluded that based on the data that I was provided, the TFA copolymer-1 molar fraction meets the limitation of percent TFA molar fraction between 2 and 20 kilodaltons.

Q. And slide 15 that is up on the screen it says TFA copolymer-1 molar fraction values Copaxone, do you see that?

A. Yes, I do.

Q. What is shown in this slide, Dr. Grant?

A. This slide is showing the results of the calculations that I made and in all cases the molar fraction, the TFA molar fraction between 2 and 20 kilodaltons is above 90 percent.

MR. JAMES: Your Honor, plaintiffs would offer into evidence under Rule 1006 slide 15 as a summary of the calculations Dr. Grant performed.

MR. ACKER: No objection your Honor.

MR. JONES: No objection.

(Plaintiff's Exhibit Slide 15 received in evidence)

Q. On the basis of that, Dr. Grant, did you make a determination as to which of the TFA molar fraction limitations were met by Copaxone?

A. Yes, all the limitations were met by Copaxone. In fact, there's one limitation that's listed here as trifluoroacetyl copolymer-1 having 75 percent of its molar fraction within the [1476] molecular weight range from about 20 kilodaltons to about 20 kilodaltons and all of the batches meet that limitation.

Q. I think I made a mistake earlier. There's a slide that I skipped over. If we could go back to the molar fraction limitations for Copaxone. Dr. Grant, what is shown on slide 10, it's entitled copolymer-1 molar fraction limitations for Copaxone. What's shown there?

A. This slide shows the results of my calculations for the percent molar fraction between 2 and 20

kilodaltons and percent molar fraction above 40 kilodaltons for these five batches of Copaxone.

MR. JAMES: Your Honor, I think what I failed to do was to offer this slide into evidence, slide 10 into evidence, under Rule 1006 as a summary of Dr. Grant's calculation.

THE COURT: Any objection?

MR. ACKER: No objection, your Honor.

MR. JONES: No.

(Plaintiff's Exhibit Slide 10 received in evidence)

Q. Have you reviewed data from Mylan regarding molecular weight characteristics of Copaxone?

A. Yes, I have.

Q. Did you review data in their ANDA concerning the molecular weight characteristics of Copaxone?

A. Yes.

Q. Based on the data that you were provided by Mylan, could [1477] you make a determination as to whether Copaxone meets the molecular weight limitations of the patents in suit?

A. Yes, I could.

Q. Did you make a determination as to whether Copaxone meets the average molecular weight limitation?

A. Yes.

Q. And what did you conclude?

A. My opinion was that Copaxone meets the average molecular weight limitations.

Q. And were you able to make a determination as to whether Copaxone, based on the Mylan data, meets the copolymer-1 molar fraction limitations and the TFA copolymer-1 molar fraction limitations?

A. Yes. Based on Mylan data, Copaxone meets both of those limitations.

MS. BLOODWORTH: Objection, your Honor, I don't know what Mylan data they're referring to, but we're willing to stipulate to the slides that Dr. Grant has gone through for the Sandoz data that's already been discussed.

MR. JAMES: I have nothing further.

THE COURT: Is that a response to -- I don't know, where we are at?

MR. JAMES: I think he's reviewed the data, the data are in the record already and with her stipulation I think that's all that we wanted to do right now.

[1478]

THE COURT: Okay. Then why don't we take the lunch break. I'll see everybody at 2:00.

(Luncheon recess)

o0o

AFTERNOON SESSION

2:10 p.m.

MR. ACKER: Good afternoon, your Honor. May I approach with the transcripts?

THE COURT: Yes, thank you.

MR. ACKER: May I proceed, your Honor?

THE COURT: Yes.

CROSS-EXAMINATION

BY MR. ACKER:

Q. Good afternoon, Dr. Grant.

A. Good afternoon.

Q. Let me start by asking you a little bit about your experience with copolymer versus the scientists who were working with copolymer-1 in the 1986 to 1994 time frame. You would agree with me, wouldn't you, that the inventors of these sort of patents that worked with copolymer-1 in the 1970's at the Weizmann Institute have more experience than you do in attempting to determine its molecular weight?

A. By its, you mean copolymer-1?

Q. Yes, sir.

A. I have not determined molecular of copolymer-1.

[1479]

Q. Isn't it also true that the scientists at Teva between 1986 and 1998 were trying to determine the molecular weight of copolymer-1, they also have more experience than you do in attempting to determine copolymer-1's molecular weight, correct?

A. I have not attempted to determine the molecular of copolymer-1.

Q. But they did, correct?

A. Yes, they did.

Q. So they have more experience than you, right?

A. They attempted to determine the molecular weight and I haven't.

Q. And you were in court on Friday when Dr. Scandella testified, right?

A. Yes.

Q. And you agree that Dr. Scandella is an expert in size exclusion chromatography, don't you?

A. I don't know that Dr. Scandella's work that much to be able to say.

Q. And after hearing his testimony, hearing his credentials, you would agree, wouldn't you that he's an expert in size exclusion chromatography?

A. No, I wouldn't.

Q. And you would agree, wouldn't you, that the inventors of the asserted patent Drs. Teitelbaum, Sela and Arnon from the [1480] Weizmann Institute are persons of skill in the art in this case?

A. I don't know. That's why, I don't know them so I can't say.

Q. You've read the '550 patent, correct?

A. Yes.

Q. You've read the articles they've written?

A. Some of them.

Q. You understand they're the inventors of the asserted patents in this case?

A. Yes.

Q. And it's your testimony that you don't know that they're persons of skill in the art, correct?

A. That's right.

Q. Isn't it true that also the scientists at Teva who attempted to determine the molecular weight of copolymer-1 between 1986 and 1998, those scientists were also one of skill in the art, correct?

A. I didn't know the scientists. I don't know what their qualifications are.

Q. Well you've read the documents as you testified on direct examination regarding the credentials, right?

A. I read some of the documents.

Q. You know Dr. Varkony, senior scientist at Teva, worked on the problem of determining molecular weight at Teva, right?

[1481]

A. Do I know Dr. Varkony?

Q. No, he is a scientist at Teva between 1986 and 1998 was working on the problem at Teva to try to determine the molecular weight of copolymer-1, right?

A. I'm not sure I'm familiar with everything that Dr. Varkony did.

Q. I asked you if you knew he was one of the scientists at Teva working on the problem.

A. I knew he was a scientist at Teva.

Q. You know Dr. Varkony has an PhD in organic and physical chemistry?

A. I didn't know that.

Q. You know that Dr. Gad was also a scientist at Teva who was working on this problem of determining the molecular weight of copolymer-1, right?

A. I've seen Dr. Gad's name.

Q. And you knew he was working on the issue of attempting to determine the molecular weight of copolymer-1, correct?

A. I think later on he was working on some aspect.

Q. And Dr. Gad had a doctor of sciences, the equivalent of a PhD in membrane fusion, correct?

A. I don't know what Dr. Gad's credentials are.

Q. And Dr. Gad is the inventor on the Gad patent that patented the peptide markers, the synthetic peptide markers that Teva now uses to calibrate the SEC column to measure copolymer-1, [1482] right?

A. I know Dr. Gad is named on that patent.

Q. He would be one of skill in the art, wouldn't he?

A. I don't know Dr. Gad.

Q. Based on what you know that he's done, including developed the peptide markers that Teva now uses to measure the molecular weight of copolymer-1, you still wouldn't agree that he's one of skill in the art?

A. The Court has defined what one skilled in the art is and I don't know that he meets the qualification. I haven't looked into it.

THE COURT: Dr. Grant, would you do me a favor and keep your voice up a little? I'm having trouble hearing you.

THE WITNESS: I'm sorry.

THE COURT: That's okay.

Q. I want to ask you a little about the '550 patent. As I heard your direct testimony, your opinion is that the '550 patent does not disclose copolymer-1 with a molecular weight of 10 kilodaltons, is that correct?

A. That's correct.

Q. And it's true, isn't it, that in the prosecution of the patents in this case, Teva took the exact opposite view, isn't that right?

A. I don't agree.

Q. If we could go to PTX 17, it's in your binder there in [1483] front of you. We'll also put it up on the screen, which is the prosecution history of the asserted patent. We'll go to 304384 and in the prosecution of one of the patents in suit Teva took this position: "The '550 patent teaches a copolymer-1 with a minimum molecular weight of 10 kilodaltons." Do you see that?

A. I see it.

Q. And it's your opinion that this statement by Teva to the Patent Office was wrong?

A. Well, I mean, I see the statement and it was written there probably by their patent lawyers, but I don't get that conclusion from reading the '550 patent.

Q. So your opinion in this lawsuit differs from the opinion that Teva's patent lawyers took in front of the PTO when they were prosecuting the patents in suit, correct?

A. I don't see an indication in the '550 patent that that's the case.

Q. And my question is, though, your opinion is different than what Teva told the Patent Office when trying to get claims allowed in the patents in this case, right?

A. My opinion is that the '550 patent does not teach a molecular weight of 10 kilodaltons.

Q. And the fact that Teva has taken this position in the Patent Office doesn't change that opinion, right?

A. That's correct.

Q. And Dr. Teitelbaum, one of the inventors of the '550 patent [1484] in his 1971 article, DTX Exhibit 1221, reports measuring the molecular weight of copolymer-1 of the Weizmann Institute using ultracentrifugation, correct?

A. Yes.

Q. We looked at that article, we looked at that article on direct examination, first sentence, this is Dr. Teitelbaum, the other inventor's article, when they talked about the work they've done at the Weizmann Institute, and if we could go to Section 3.7, Section 3.7 discusses the way in which the molecular weight was determined at the Weizmann Institute and it was done by ultracentrifugation, correct?

A. That's what it says.

Q. And you agree with that, right?

A. I agree that's what it says.

Q. And you agree that the copolymer-1 that was measured at the Weizmann Institute, its molecular weight was measured, was done by ultracentrifugation?

A. Yes.

Q. And ultracentrifugation would give you either a Z molecular weight or a weight average, correct?

A. Among others.

Q. And as you testified just a little bit ago, weight average for copolymer-1 would be higher than peak average for copolymer-1, correct?

A. That's correct.

[1485]

Q. And if we could bring up the chart, PTX 982, just so the Court understands despite the fact that the Mz and Mw are lower on the chromatogram because they came out on the column first they have a higher molecular weight, right?

A. They do.

Q. And so it's your opinion that both Mz and Mw for copolymer-1 would be larger than peak average, right?

A. Yes. But Mn is smaller.

THE COURT: I'm sorry, than what?

THE WITNESS: Mn is smaller than peak average.

THE COURT: Thank you.

Q. So the types of molecular weight measured by ultracentrifugation, Mw, and Mz at the Weizmann Institute, those molecular weight readings would be higher than peak, correct, for copolymer-1?

A. Yes, but there's information in the literature that you can also determine Mn.

Q. So the Z and weight averages for the copolymer-1 underlying the '550 patent, those would be higher than the peak average for that copolymer-1 right?

A. In general, the Mz and Mw would be higher than the Mp.

Q. And that would be true for the copolymer-1 that was measured at the Weizmann Institute that underlies the '550 patent, right?

A. In general, I would think so.

[1486]

Q. Now, certain claims of the asserted patents use the word "about" when referring to certain molecular weight ranges, correct?

A. Yes.

Q. And in your opinion the word "about" expands the claimed molecular weight ranges in the vicinity of plus or minus 10 percent, right?

A. Well, I'm not qualified to give a legal opinion of "about," but I have expressed the opinion that there's variability in size exclusion chromatography of approximately 5 to 10 percent.

Q. So in your opinion the word "about" would expand 5 to 9 up to 9.9, correct?

A. It could.

Q. And it would expand the lower range 5 down to 4.5, correct?

A. In the variability of the instrumentation.

Q. And that would be true for all the claims of the asserted patent where the word "about" is used before a molecular weight range, right?

A. The word "about" would expand those interpretations yes.

Q. Wherever it's used in the asserted patents, right?

A. As far as I understand it.

Q. Now, you talked about a couple of methods to calibrate an SEC column during your direct examination. You talked about fractionation and you also talked about polymer standards, correct?

[1487]

A. I talked about both of those things, yes.

Q. But in each of those instances, whether you were to fractionate to get your standards of copolymer-1 or you were just to make additional batches of copolymer-1, you would have to use a different alternative method to measure the molecular weight of the standards, right?

A. Yes.

Q. I mean, in other words, we talked about this a little bit last week, but in order to be a known

standard you have to know the molecular weight, correct?

A. That's correct.

Q. And so the idea of a self-standard is you get a sample of a sample that you're going to measure and then you determine its molecular weight by a different analytical technique, right?

A. Yes.

Q. And you've already testified that you could use MALLS, viscometry, ultracentrifugation and mass spectrometry to measure the molecular weight of a self-standard, right?

A. Yes.

Q. But depending on the method used to measure the molecular weight of the self-standard you may get a different type of molecular weight, right?

A. You may.

Q. For example, if you use osmometry to measure you get number [1488] average molecular weight, right?

A. Yes.

Q. And if you use light scattering to measure you get weight average molecular weight, correct?

A. Yes.

Q. And if you use viscometry, that will give you a viscometry molecular weight, correct?

A. A viscometry average molecular weight.

Q. And if you use ultracentrifugation as we discussed you could get weight average or Z-average?

A. Or number average.

Q. And it's true that those different types of molecular weights; number, weight, viscosity and Z may all be different for the exact same sample or standard, right?

A. The numerical values may be different.

Q. Now, let's take a look at the '808 patent and we can go to column 3, lines 6 to 8. I think Mr. James showed this to you on direct. Now, these words, "The molecular distribution of two batches determined on a calibrated gel filtration column (Superose 12)," this is the description of the method used by the inventors of the '808 patent to obtain the molecular weights of the two batches of copolymer-1 in example 1 of the patent, right?

A. Yes, that's what it says.

Q. And that's the entire description in the specification, [1489] right?

A. Yes.

Q. And we know Superose 12 is a type of SEC column, right?

A. Yes.

Q. But there's no disclosure in any of the patents of what type of standards should be used, right?

A. That's correct.

Q. And there's no disclosure of the standards Teva used before 1995 to calibrate the SEC column to determine the molecular weight of copolymer-1, right?

A. That's correct.

Q. And there's no mention of using self standards at all in any of the patents, right?

A. They don't mention self standards as such.

Q. And if one on his or her own were to decide to use self standards, there's no guidance in the patent as to which of the different analytical techniques one should use to measure the molecular weight of those self standards, right?

A. No, it's not necessary.

Q. And there's no disclosure of the various analytical methods that Teva used between 1986 and 1988 to measure the molecular weight of its cop-1 self standards, true?

A. Disclosure in the patent?

Q. Yes, sir.

A. No, there is not.

[1490]

Q. Now, you talked a little bit in questioning from Mr. James about this correlation technique that you pointed to in the literature. As I understand your testimony you believe it is a technique that would allow you to take one of these different types of averages, whether it be a number average or a weight average or a Z-average, and convert it to peak average for your standard. Do I have that right?

A. Yes, in essence.

Q. But it's true, isn't it, that there's no mention in any of the patents of a need to do this type of correlation, right?

A. The patents don't mention it.

Q. And there's no mention in the patents of what type of weight one should start at, that is, what analytical technique one should use to measure the standards so you know what type of average you're starting with so you could get back to peak; that's not mentioned at all, right?

A. I don't know if I got all that. Could you repeat it?

Q. Sure. There's no mention in the patent that viscometry should be used to get a certain type of molecular weight, correct?

A. Correct.

Q. And there's no mention of any other analytical technique that should be used to get another type of molecular weight, right?

A. Right.

[1491]

Q. And there's no mention that because you used those different types of methods you need to correlate back to peak, right, that's not talked about at all?

A. Doesn't say that.

Q. And it's true that Teva itself it never correlated any of its molecular weight readings for its standards back to peak, isn't that true?

A. That's not exactly true.

Q. Why don't we take a look at DTX 1192? If we could go first to -- if you prefer the screen that's great, sir, but there's also a binder for that. If you go to 1162279.

A. Could you give me the DTX number again, please?

Q. 1192.

A. Okay. And page?

Q. 1162279.

A. Okay.

Q. You see this is a memo from Grace, Teva's contractor dated March 5, 1992, and the subject line is MALLS, molecular weight determination of cop-1. Do you see that?

A. Yes.

Q. And you know cop-1 to be the term that was used for the self standards that were used inside of Teva to calibrate SEC column, right?

A. That term has been used for the self standards, yes.

Q. We go to the first sentence of the memo. It reads, "You [1492] submitted ten batches of cop-1 for molecular weight determination using multiple angle laser light scattering or MALLS." Do you see that?

A. Yes.

Q. You understand that that was a technique that Teva was using in March of 1992 to measure the molecular weight of the self standards, right?

A. Well, it's a technique that Grace was using.

Q. So Teva farmed this work out to Grace and Grace used MALLS to measure the molecular weight of a batch of self standards, right?

A. That's what it says, yes.

Q. If we go to the next page 1162280 and you see on the left of the column we have a list of a number of self standards those are cop-1 self standards, correct?

A. Yes.

Q. And there's ten of them, correct?

A. There are ten shown, yes.

Q. And then you can see across the columns there, Grace provided Mn values, Mw values and Mz values for each of the ten, right?

A. Yes.

Q. And it measured each one of the cop-1 standards three times, right?

A. Well, there's three entries for each of them here.

[1493]

Q. And if we go back now to 1162278, it's one page back, sir.

A. I see it.

Q. And you see there's a Teva pharmaceuticals document there and it says molecular weight of cop-1 standards. Do you see that?

A. Yes.

Q. And you see the first standard R187. If we could highlight all the way across, please? And it's given an exact measurement there of the molecular weight of that standard of 37,266 daltons. Do you see that?

A. I see it.

Q. And if we put the split screen up, and it's true, isn't it, that what Teva did was they simply added up the three molecular weight values for the Mn value, for the standard. If we start with the first one, R187, and they just divided by three, right?

A. Well, I'm not sure what they did, but the value is consistent with them having done that.

Q. I've got a calculator --

THE COURT: He's not disputing your figures.

MR. ACKER: Okay, great.

Q. So the only value that they used was the Mn value, right?

A. Well, they reported the Mn value.

Q. In their listing of what the molecular weights were of their cop-1 standards they've simply just taken and used the Mn [1494] value, right?

A. Those numbers seem to be consistent with the numbers in the table.

Q. And they didn't do anything with the Mw values or the Mz values, correct?

A. Not in this table.

Q. And there's nothing in the patent that says that Mn value is the right value that should be used, correct?

A. The patent does not state that.

Q. And there's no conversion here of the Mn value to what would be the correlating Mp value, right?

A. Not at this point.

Q. And it's true, isn't it, that these are the molecular weights that were used inside of Teva on the left side, the average of three Mn values, to calibrate the SEC column to measure the molecular weight of copolymer-1?

A. Based on this I'm not sure how they used them.

Q. You just don't know, correct? But you would agree with me that in this listing of the molecular weight of the copolymer-1 self standards there is no conversion of the Mn value to an Mp value, correct?

A. Not here.

Q. And did you see any document at any point in your work in this case where there was a conversion of Mn values or Mz values or Mn values to Mp values?

[1495]

A. Yes, I saw a document where it was attempted.

Q. Just attempted though, right?

A. No, I didn't look at all of the documents.

Q. So when you were testifying on direct about this correlation that would take place that would move these Mn and Mz values to other values, you

never saw a document that explained that being done inside of Teva between 1986 and 1988, right?

A. It's what a person skilled in the art would do.

Q. My question was did you see any documents inside of Teva showing that that is what took place?

A. I said I saw a document where they attempt to do a conversion.

Q. Now, in 1987, the scientists at Teva used commercially available globular protein standards to calibrate an SEC column to measure the molecular weight of copolymer-1, right?

A. I disagree.

Q. All right, let's take a look at the document you disagree about. Could we bring up 3275, please? Now, you testified on direct that it was your understanding from review of the document that the only thing that happened in this experiment was the column was tested using globular proteins but it wasn't actually calibrated using globular proteins. Do I have that testimony right?

A. What do you mean by the only thing that happened?

[1496]

Q. Well, you testified that you dispute -- well, let me just ask the direct question. Isn't it true that this document shows that the scientists at Teva in 1987 used globular proteins to calibrate an SEC column to measure copolymer-1?

A. I disagree.

Q. Okay. So let's take a look at the section 2.5. We go first to, yes, section 2.5. Do you see 2.5.1, you go into the document there's a listing there of the reagents, right?

A. What do you mean by reagents?

Q. If you could go up a little higher on the document. 304991. Do you have that page?

A. Yes.

Q. And if you could go, do you see in the section labeled 2, it says reagents?

A. Okay, yes.

Q. And down below for the molecular weight calibration standards in 2.5 there's a listing of globular proteins, right?

A. Those are globular proteins.

Q. And then if we go to section 4.1 on 304993, under section 4.1 it says molecular weight calibration curve, do you see that?

A. I see that.

Q. And what were the standards that were used to set this calibration curve at Teva in 1987?

A. Well, I had indicated that this was not a correct label, [1497] but these standards were globular proteins.

Q. So in the Teva document of August 3, 1987 it says what the standards that were used and they were proteins, right?

A. These are proteins.

Q. But you disagree with what the description in the document, do I have that right?

A. I disagreed that they used them to calibrate the column.

Q. Why don't we take a look at the results at paragraph 6 going from 304994 to the next page and we start at the bottom of 304994 and read over to the other side. It says, "The molecular weights of cop-1 batches," and we know those are copolymer-1 standards, right?

A. I'm not seeing it.

THE COURT: It went off screen.

MR. ACKER: We'll get it back.

Q. "The molecular weights of cop-1 batches," we know those were cop-1 standards, right?

A. Yes.

Q. "Calculated from the calibration curve of markers, figure 1, were four to five times higher than those obtained by viscosity and ultracentrifuge." Do you see that?

A. I see that.

Q. And if you go down to the see the sentence that begins with "cop-1"?

A. Okay.

[1498]

Q. And it reads, "Cop-1 is a highly charged linear polymer while the markers used in this study are globular proteins," right?

A. That's right.

Q. And yet you disagree that proteins were used at Teva in 1987 to calibrate an SEC column?

A. That's correct. They determined that they were not appropriate.

Q. But in this initial preliminary analysis, the first thing they did was they used the proteins to calibrate the column, right?

A. They may have done it initially, but they determined they were not appropriate and they abandoned it.

Q. So when you testified on direct examination that they were not used, the proteins were not used to calibrate the column, that testimony was not correct?

A. I meant they were not used over an extended period of time.

They did not rely on them.

Q. But that's not what you said. What you said was they weren't used.

THE COURT: All right, I can read the transcript.

MR. ACKER: I understand.

Q. And why don't we take a look at 304996. You see that's the figure 1, if we can blow that up. That's the calibration curve that we just looked at, right, that was just referenced?

[1499]

A. It's a curve that lists globular proteins.

Q. Well what's it say on the bottom, figure 1?

A. It says, "Gel filtration on Superose 12 calibration curve."

Q. And the standards that are used in this figure 1 calibration curve are proteins, right?

A. Yes, but they're not appropriate.

Q. But the question is, isn't it true that the scientists at Teva when they initially set out to measure copolymer-1 in 1987 attempted to do it with these protein standards calibration curve, isn't that right?

A. I think they looked at them and decided they were not appropriate.

Q. And if we go to the results section -- well, what the document shows is that Teva got results using SEC with the protein standards that were much higher than the prior results using ultracentrifugation and viscometry, right?

A. That's what it shows.

Q. But if one skilled in the art did not have the benefit of those viscosity and ultracentrifugation molecular weight readings for copolymer-1 that Teva had internally, they would not know that the results obtained using the proteins to calibrate the column were too high, would they?

A. I disagree.

Q. And those readings, that is, the viscometry and the ultracentrifugation molecular weight readings, that was not [1500] publicly available information in 1987, right?

A. Teva's internal documents?

Q. Yes.

A. I do not believe that it was public.

Q. And that information, the viscometry and the ultracentrifugation readings, that information was not disclosed anywhere in the patents, right?

A. I think that's correct.

Q. And there was no mention in the patent that you shouldn't use proteins because you're going to get readings that are too high, right?

A. No, the patent didn't say that.

Q. Why don't we take a look at PTX 981, please?

A. Okay.

Q. Do you have that?

A. Yes, I do.

Q. Actually, let's skip over that one. Let's go to DTX 1762.

A. Okay.

Q. This is a document that you looked at with Mr. James on direct examination, correct?

A. Yes, it looks familiar.

Q. And it's a May 4, 1988 memo from Teva's consultant back to Teva regarding their attempt to measure the molecular weight of copolymer-1, right?

A. That's right.

[1501]

Q. And if we take a look at the first sentence, you see they're measuring two cop-1 batches or two standards, right?

A. Batches 13 and 11A.

Q. And you understand that Teva hired W.R. Grace to try and characterize copolymer-1 including determining the molecular weight of these two batches, right?

A. I'm not sure why they hired W.R. Grace.

Q. And W.R. Grace in this study, in this first experiment in 1988 used commercial available protein standards to calibrate the SEC column, right?

A. A large part of this is redacted.

Q. Why don't we go to page 4, second bullet point.

A. Which page?

Q. Page 4. It's up on the screen too, if that's more helpful.

A. Okay.

Q. And you see the memo from W.R. Grace back to Teva reads, "Calibration curves based on globular proteins yield cop-1 molecular weights four to six times higher than molecular weights calculated by ultracentrifugation or viscosity measurements."

A. I see that.

Q. So, again, W.R. Grace, like the scientists at Teva when they first started out measuring copolymer-1 using SEC, calibrated the columns using globular proteins, right?

A. W.R. Grace did that.

[1502]

Q. Again, they also determined that the readings were too high because they had the benefit of Teva's ultracentrifugation and viscosity measurements of the same batches, right?

A. Well, they were able to determine that they were too high, yes.

Q. Well, higher than the molecular weights calculated by ultracentrifugation or viscosity, right?

A. That's what it says.

Q. Because they had the benefit of that data, right?

A. Well, if they knew they were too high, they must have had the data.

Q. And if we go to page 8, this is what they found out in this experiment for these two batches, correct, that the high readings were obtained when they used proteins and the viscosity readings were much lower, right?

A. Yes, the inaccurate readings were when they used the proteins.

Q. After Teva did this work, the suggestions back from W.R. Grace, the suggestion back from W.R. Grace to Teva was not to use self standards or not to use proteins, right?

A. I'm not sure what they recommend. Could you point that out?

Q. Sure. Could we go to 17? And bullet point 3, and it's on the screen. They didn't recommend self standards, right?

A. No. They recommended alternative calibration standards.

[1503]

Q. Commercially available calibration standards, right?

A. Doesn't say commercially available.

Q. But you know that's true, right?

A. Probably were.

Q. So W.R. Grace tries proteins, they get readings that are too high and they don't say you have to use self standards, right?

A. They don't say that.

Q. They don't say you should use universal calibration, correct?

A. They don't say that.

Q. They say let's try some other commercially available materials to use as standards, right?

A. They say they can be investigated.

Q. Why don't we go to DTX 3538 and this is more work by Grace in May of 1988, correct?

A. It's dated May 1988 and it is a memo.

Q. If we look at the summary, the first paragraph there on the document, you see they're also measuring two cop-1 standards, right?

A. Yes.

Q. And it says, "I have completed molecular weight determinations of cop-1 batches 11A and 13 using a TSK G3000 SW size exclusion column calibrated with polyethylene glycol (PEG)." Do you see that?

[1504]

A. I do.

Q. And PEG were also another commercially available standard in this time frame 1988, correct?

A. Yes.

Q. So now we've seen the next attempt by Grace; again. They don't suggest to measure these cop-1 standardards, let's use self standards, right?

A. I don't see that mentioned.

Q. They don't say let's use universal calibration, right?

A. I don't see that.

Q. They say let's use some other commercially available standards to calibrate the column, right? They suggest PEG.

They say we're going to use PEG.

A. Well, they used PEG.

Q. Even better, they used PEG, right?

A. That's what it says.

Q. Let's take a look at the results. If we could go to the next page. And if we go down to the bottom of that page, the second page of the document and over to the top of the third page of the document. And if we could highlight the tables at the bottom and then

the top of the third page. So in the readings they actually got, if you look at the PEG reading done by Grace was 7400 daltons, right?

A. That's what it says.

Q. And their conclusion, if you go up to the top, on the top [1505] of page 3 is cop-1 molecular weights based on polyethylene glycol calibration curves are consistent with those determined by viscosity measurements at Teva, do you see that?

A. I see that.

Q. So here we are in the same time frame, one time using commercially available proteins results in standards that are really much too high, correct, in the prior document?

A. The protein standards.

Q. Yes.

A. Yes.

Q. And then here they're using PEG which are another commercially available standard, that is, W.R. Grace are and they're getting readings for this cop-1 standard that at least they think is consistent with what was obtained using viscosity, right?

A. At this time.

Q. And so it's still your opinion, though, that it would have been a bad idea in this time frame in 1988 to use commercially available standards to attempt to calibrate a column to measure the molecular weight of copolymer-1, right?

A. My opinion is it would have been inappropriate to use standards that wouldn't give you an accurate molecular weight.

Q. Let's move to DTX 1269. Do you have that?

A. Yes, I do.

Q. And this was also a document that you looked at again on [1506] direct examination with Mr. James, correct?

A. Yes.

Q. And you recall that in this document there was a fractionation of a copolymer-1 sample, right?

A. A fractionation by ion exchange.

Q. A column was used to measure the molecular weight of those fractions, right?

A. That's correct.

Q. But there was also an alternative method that was used, correct?

A. I'm not sure what you mean by alternative.

Q. Well, viscometry was used, right? Or vapor phase osmometry was used, correct?

A. It does mention vapor phase osmometry.

Q. If we go to that section of the document, it's 1095158.

A. Okay.

Q. So this is again Teva's outside consultants in September of 1988 and so far they have tried protein standards and PEG standards, right?

A. Yes.

Q. And now they're trying another method, vapor phase osmometry, correct?

A. Yes.

Q. And this is a standard, a method, an analytical method that you believe was appropriate to attempt to measure the molecular [1507] weight of standard during this time frame, right?

A. No, I don't agree.

Q. Isn't it true you testified not more than 15 minutes ago that VPO osmometry was an appropriate method to attempt to measure the molecular weight of standard?

A. No, I didn't say that.

Q. So it's your opinion that VPO would not be an appropriate method?

A. That's correct.

Q. But W.R. Grace thought it was, right?

A. I don't know what W.R. Grace thought.

Q. Well, they tried it, didn't they?

A. They did try it.

Q. And when they tried it they got a reading that was really low, right?

A. Yes.

Q. So again they tried a method that they thought was appropriate but when they compared it back to the internal readings from Teva, they realized that that method would not work to measure the standard, right?

A. They realized it wouldn't work.

Q. And again, that information that osmometry is not a good method to use to measure a self-standard to attempt to calibrate a column to measure copolymer-1, that's not disclosed anywhere in any of the asserted patents, right?

[1508]

A. Doesn't say that osmometry is not a good method.

Q. If we could go to to PTX 748. And if you could go to 305205.

A. Okay.

Q. And this is the document that highlights a protocol that was used inside of Teva to measure the molecular weight of standards beginning in the 1989 time frame continuing till about 1992, correct?

A. Well, this is dated 1989.

Q. And you know that this method was self standards were used, these cop-1 self standards, correct?

A. Could you direct me to that?

Q. Well, do you know that?

A. Yes.

Q. During this time frame that's what was happening inside of Teva?

A. In 1989 they were using cop-1 standards, yes.

Q. And they were using viscometry to measure the molecular weight of the standards, right?

A. They were at times, yes.

Q. And this method continued until 1992 inside of Teva, right?

A. Until at least 1992.

Q. But --

A. I think they were still using cop-1 standards later than that.

[1509]

Q. Let me be clear. They were still using cop-1 standards beyond that point but they stopped using viscometry to measure cop-1 standards and switched to MALLS, correct?

A. I'm not sure exactly the time point, but they did switch at some point.

Q. And the fact that between 1989 and 1992 viscometry was the method that was used inside of Teva to measure the cop-1 standard, that's not disclosed in the patents, right?

A. That's correct.

Q. Now, if we could go to 3510, PTX 3510. This is a document that Mr. James showed you on direct examination, right?

A. Yes.

Q. And you testified on direct examination that this document made clear that the earlier work that Teva had done using globular proteins to calibrate the column was just a test and they didn't actually use it to calibrate the column. That was your testimony, right?

A. They didn't use it after their initial attempts.

Q. But you testified they never used it and you relied on this document to support that opinion, right?

A. I testified that they didn't use the globular proteins because they recognized that they were inappropriate.

Q. Right, but you testified they didn't use it at all but now we've established they they in fact did.

MR. JAMES: Objection, your Honor.

[1510]

THE COURT: I only need to hear the question once, maybe twice.

Q. Yes, your Honor. Why don't we go to section C?

A. Okay.

Q. And you see this is sort of a document that sort of lays out a history of all the different techniques that Teva had tried internally to measure the molecular weight of its copolymer-1 self standards, right?

A. It doesn't say it's a history.

Q. But you've read it and you know that's what it is, it's a chronology of what's occurred, right?

A. I read it a long time ago. I'd have to reread it to be sure.

Q. Let's take a look at section C. You see section C reads, "Globular markers (proteins) and copolymer-1 samples were injected under the same conditions into Superose 12 columns.

The molecular weight of the copolymer-1 samples were calculated from the correlation between the elution volume (or retention time) and the log Mw of protein markers." Do you see that?

A. I do.

Q. Then if we could go to the next page, and let's highlight section D. And then we also see that internally at Teva one of the other options that they tried to measure the copolymer-1 standards were these PEG markers. Do you see that?

[1511]

A. They were tested as possible standards.

Q. And so inside of Teva during this time period up until 1992, the protein standards had been used used, viscometry had been used and PEG standards have been used, correct?

A. They investigated them.

Q. And then if we go to section E, you see here it says that "Histones (basic proteins) and polysines were also tested but not successfully since they showed several peaks in each sample and their elution pattern was different than that of copolymer-1," do you see that?

A. I see that.

Q. That was another attempt made inside of Teva to measure the molecular weight of copolymer-1?

A. They looked at those.

Q. None of this information about the attempts that Teva had made using different and alternative techniques was disclosed in any of the patents, right?

A. That's right.

Q. If we go to DTX 1744. Now, you testified on direct examination that you had not seen, in your review of all the documents you had not seen any evidence that Teva was struggling to determine the molecular weight of its cop-1 standards, right?

A. That's correct.

Q. And you see this is a letter dated August 29, 1995 from [1512] Dr. Krull, Ira Krull at the department of chemistry at Northeastern University in Boston, Massachusetts. Do you see that?

A. Yes.

Q. And it's written to Dr. Ilan Schwartz at Teva, correct?

A. That's right.

Q. In the analytical R&D laboratory, correct?

A. Yes.

Q. And Dr. Krull was hired as a consultant to help Teva in this time frame figure out what the molecular weight was of the copolymer-1 standards, right?

A. I don't know. I don't recall the contents of the letter.

Q. Why don't we take a look at the first sentence of the second paragraph? And what Dr. Krull in August of 1995 wrote back to Dr. Schwartz at Teva was, "At issue here is the observation that cop-1 results," and, again, those are measuring the cop-1 standards, correct? Dr. Grant?

A. It mentions cop-1.

Q. "At issue here is the observation that cop-1 results in terms of Mw or molecular weight and Mw or molecular weight distributions appear to vary from method to method and sample to sample." Do you see that?

A. I see that.

Q. So this was the information that was flowing back to Teva in August of 1995 from its outside consultants regarding the [1513] efforts to measure the molecular weight of the cop-1 standards, right?

A. Well, that's what's written here.

Q. And you have no reason to dispute that, right?

A. I don't know the reason why it was written.

Q. Why don't we take a look at DTX 3137. Do you have that in front of you, sir?

A. Yes, I have it.

Q. And this exhibit, DTX 3137 is dated July 4, 1996 and it's a letter from, if you look at the last, the third page?

A. Third page?

Q. I'm sorry, the last page of the document, it looks like.

Fifth page?

A. Okay.

Q. There we go. Do you see it's signed by a Dr. Jurgen Kettenring, do you see that?

A. Yes.

Q. He's the team leader of AR&D, do you see that, inside Teva?

A. It doesn't say Teva.

Q. If you take a look at the first page of the document you see there's a big heading on the top?

A. Yes.

Q. And the word says "Teva," right?

A. It does.

Q. Why don't we take a look at the first page of the document? [1514] And if we could highlight the second paragraph, and what Dr. Kettenring was telling others inside of Teva on July 4, 1996 was "The molecular weight for copolymer-1, which is a heterogeneous mixture of polypeptides, has been determined so far by different techniques such as analytical ultracentrifugation, SEC chromatography with light scattering detection or with a calibrated SEC column." What he wrote in July of 1996 was "Depending on the chosen analytical technique, the average molecular weight for copolymer-1 RS 03494 varies between 4700 and 11,000 daltons." Do you see that?

A. I see it.

(Continued next page)

[1515]

Q. And you know that R.S. 03494 is a particular copolymer-1 standard, right?

A. I don't recall that number.

Q. And what's going on here, what Dr. Kettenring is saying is that we keep using different methods to measure that standard, and when we use different analytical methods to measure the standard, we get different results, right?

A. He's saying that his results vary between those two numbers.

Q. And they varied when he uses a different analytical technique to measure them, right?

A. That's what it says.

Q. Now, if we take a look at the next paragraph, it reads: "Due to the complex mixture of relatively high molecular weight compounds, a new recently introduced mass spectroscopial technique matrix assisted laser desorption ionization with time of flight detection, MALDI-ToF, offers the possibility of determining the absolute molecular weight distribution of copolymer-1," right?

A. That's what it says.

Q. So inside Teva in July of 1996, the head of its R&D is saying, we still need to find another method for the possibility of determining the absolute molecular weight distribution for copolymer-1, right?

[1516]

A. I don't know that they said they still needed to.

Q. Well, used those words, offers the possibility of determining the absolute molecular weight distribution of copolymer-1, right?

A. They were looking at another method.

Q. And they were looking at another method because the methods that they had been using previously, to determine the molecular weight of their standards, were giving them varied results, right?

A. That's what it said.

Q. And that's what happened, right?

A. Well, all I know is what it said.

Q. And none of this information, that is the attempts that Teva had made with these other techniques and the varied results they were getting, or the fact that they now were going to try MALDI-ToF. none of that's disclosed in any of the patents?

A. It's not mentioned in the patents.

Q. Why don't we go to the last page or conclusion section of this document. I'm sorry, let's go to figure two, the actual MALDI-ToF experiment. It's on page 305. Do you have that, Dr. Grant?

A. Yes, I do.

Q. See the figure 2, this is the description of the efforts to use MALDI-ToF to measure that same standard, that same batch, [1517] that same cop-1 standard, right?

A. Figure two is not MALDI-ToF

Q. Right. But what the heading says is "SEC chromatogram with MALLS detection of copolymer-1 R.S. 03494 Mw distribution," correct?

A. That's what it says.

Q. And then it reads: "The numeric average molecular weight Mn, obtained by the MALDI-ToF experiments, is much lower than the value determined by the chromatographic method with MALLS detection, 4,000 daltons versus 10,000 daltons, or versus ultracentrifugation, 7,000 daltons." You see that?

A. I see that.

Q. So the use of MALDI-ToF didn't work out, right?

A. Not in this one experiment.

Q. And, again, that's not information that was disclosed anywhere in the patents, right?

A. That's right.

Q. If we go to the conclusion section of the document, Dr. Kettenring sums up -- blow up the first paragraph, please -- "molecular weight values for copolymer-1 R.S. 03494 determined by traditional analytical methods such as light scattering, ultracentrifugation or SEC chromatography are in the range of 7,000 to 11,000 daltons. The differences are due to the experimental bias of the analytical technique and how data are calculated and presented. Therefore, it should be explicitly [1518] stated by which analytical method the molecular weight data were obtained."

That was the conclusion inside Teva in 1996, right?

A. That's what this paragraph says.

Q. And they take a look at the next paragraph. "Molecular weight values for copolymer-1 determined by MALDI-ToF experiments are considerably lower

than those obtained by traditional analytical techniques." Do you see that?

A. I see that.

Q. Again, so they tried another method and they got results they thought were inconsistent with the methods they used previously, correct?

A. Based on this one run.

Q. And, in your opinion, is mass spectrometry is an appropriate method to measure the molecular weight of copolymer-1?

A. It can be if done properly.

Q. And so it's your opinion that although they tried that technique here, they didn't get the results they want -- they didn't do it properly?

A. That's a possibility.

Q. But you don't know, right?

A. I wasn't there, so I don't know what they did.

Q. Yet, it's your opinion that Teva was having no problems, and you've seen no documents determining or evidencing that [1519] Teva was having problems determining the molecular weight of its copolymer-1 self standards, right?

A. My opinion is that Teva used cop-1 standards as early as 1987 and continued using them. What they were doing otherwise were probably for other reasons.

Q. Why don't we look at DTX 1706?

A. Could I have the number again, please?

Q. 1706. And if you go to page 1013050. So take a look this -- this is an internal document from Dr. Varkony to his colleagues on April, 1996. And he writes to them: "Attached, please find some questions, suggestions and speculation on molecular weight determination of copolymer-1." Do you see that?

A. I see it.

Q. And if we go to the next page, you see there is a list of 16 experimental and conceptual errors in MALLS; do you see that?

A. I see it.

Q. And at this time frame in 1996 MALLS was the technique that Teva was using to measure its cop-1 or copolymer-1 self standards, right?

A. I believe you stated that before, yes.

Q. And at this point in '96 Dr. Varkony is writing to his colleagues saying there are experimental and conceptual errors in that technique, right?

[1520]

A. That is true of any technique.

Q. You see some of those errors or problems that they're having inside Teva, include number eight, "Alex's report on correlation of molecular weight with RRT, indicates that for the same RTT, the range of molecular weight can be few hundreds or even thousands of daltons."

That was a problem they were having with MALLS, right?

A. Well, that's what it says. I don't know that it's a problem.

Q. Then you look at ten says, "Is the problem related to experimental conditions or to interpretation in calculation?

Do you see that?

A. I see it.

Q. So Dr. Varkony is speculating on what is causing the problem with using MALLS to measure the cop-1 standards, right?

A. He is speculating.

Q. And then he says, number 11, "Is the problem present only in copolymer-1 or also in some of the globular markers?" Do you see that?

A. I see it.

Q. And you see on the page, if we could blow the page up, the whole page, the whole thing under the heading Experimental and Conceptual errors in MALLS, Dr. Varkony is writing his colleagues with 16 issues that need to be addressed; you see that?

[1521]

A. I do.

Q. Now, in 1988 Teva switched methodology for measuring molecular weight of copolymer-1 another time, correct?

A. What are you referring to?

Q. Well, they switched they began using synthetically created peptide standards, right?

A. In 1988.

Q. Yes, 1998. Sorry.

A. Okay.

Q. You agree with that?

A. Somewhere around that time.

Q. So let's take a look at 3507?

A. DTX?

Q. Yes, sir. And just to set the chronology, in 1992, Teva stopped using viscometry to measure its cop-1 standards and began to use MALLS, correct?

MR. JAMES: Perhaps you could use the --

MR. ACKER: If we could put it on the private screen, please.

A. Could you repeat the question?

Q. Sure. The first measurement of cop standards after the initial stage was viscometry, right?

A. They were using viscometry.

Q. Then in 1992, they switched to using MALLS, correct?

A. They switched around that time, yes.

[1522]

Q. And then what we're going to look at now, in 1998 Teva switched again to using the Gad synthetic polypeptide standards, right?

A. They started using them around that time.

Q. And then you see the first page is a letter from Teva to the FDA, August 31st, 1998. You see that?

A. Yes.

Q. And if you look at the second paragraph there, it says, "Found in Attachment i is a report with pendency A1 and 2 providing data and rationale in support of this addition of molecular weight markers prepared by solid phase synthesis for determination of the molecular weight of glatiramer acetate," right?

A. That's what it says.

Q. And at this point Teva is switching to using these standards, the Gad standards because -- and they made -- the switch was made because of the FDA's doubts about the accuracy of the molecular weight values Teva obtained using its old markers of copolymer-1 measured by MALLS, correct?

MR. JAMES: Objection, your Honor. I don't think there is foundation for that.

THE COURT: All right.

MR. ACKER: He said he reviewed the documents regarding this, so I'll show him where it says that.

THE COURT: You can show him a document and ask him.

[1523]

Q. Okay. Let's take a look at the Teva 000213922, and take look at the second, the first full paragraph down at the bottom. You see the words, the paragraph the sentence that begins with the words, "the term." Do you have that, sir?

A. No, I don't.

Q. Are you on 213922?

A. 213922.

Q. See the second full paragraph there, two paragraphs above the word approach, above the heading approach?

A. Yes.

Q. If you go to the last sentence of the paragraph just above the section two. Do you have that?

A. The term, okay.

Q. And it reads "The term determination with respect to molecular weight was changed to estimation, in response to FDA's express doubts about the accuracy furnished by a calibration based on glatiramer acetate markers." You see that?

A. I see that.

Q. So it was true that in 1998 Teva changed again from using cop-1 self standards to using the Gad peptide standards, because the FDA had expressed doubts about the accuracy of the molecular weights obtained using the cop-1 self standards, right?

A. The FDA expressed that they would like to have them changed, yes.

[1524]

Q. And that change was made, correct?

A. Yes, I believe it was.

Q. And if you take a look at TEV213933. Do you have that, sir?

A. Yes.

Q. And you take a look at the paragraph there beginning at the top, there was a study done comparing the molecular weights that were obtained

using the old cop-1 self standards and the new synthetic polypeptide standards, right?

A. Yes.

Q. And the first sentence there, the results of the study reported where it says, "The calibration based on the new polypeptides was compared to the currently used calibration based on glatiramer acetate molecular weight markers, tab (Table 3B), The molecular weights obtained using the two calibration tests within the specification range differed by typically not more than 20 percent. You see that?

A. I see it.

Q. So what they're telling the FDA, Teva is, in 1998, is we're now measuring our standards using the new methods, the synthetic polypeptide method comparing it to the cop-1 method we had been using and we're off by between 12 and 20 percent, right?

A. They said they thought they weren't significant, and the FDA accepted it.

[1525]

Q. But the percentages they gave for the differences were between 12 and 20 percent, right?

A. That's what it says.

Q. And that was in 1998, correct?

A. That's the date on the letter.

Q. And the peptide standards, the synthetic peptide standards, Gad markers, are not disclosed in any of the patents, right?

A. Not in the patents in suit.

Q. In fact, they didn't even exist until after the patent in suits were filed, right?

A. If the date is 1998, patents in suit were filed in 1994.

Q. Let me show you PTX-431. Do you have that? If you could bring that up?

This is a graph that you prepared, correct?

A. That's right.

Q. And you prepared this graph based on some readings that had been obtained or molecular weight determinations that had been obtained for a number of 15 different cop-1 self standards, right?

A. I don't remember the numbers 15, but it was cop-1 standards.

Q. And the different methods that those cop-1 standards were measured was using viscometry, ultracentrifugation and MALLS, right.

A. That's right.

Q. And the purpose of this graph was to show that, in your [1526] opinion, you get the same result regardless of which method you used to measure the self standards, right?

A. No. The purpose of the graph was to see what the data showed.

Q. And that was your conclusion, right?

A. My conclusion was, is that all three of those methods produced linear regression fit that superimposed on each other.

Q. And if you take a look at DTX-3509, and if we go to the table that Dr. Grant used at 1111617. If we could blow that up.

And we looked at this a little bit when you testified last week. But these were the numbers, the different values for molecular weight readings of the cop-1 standards that you plotted on your graph, right?

A. Yes.

Q. But these numbers in this table one in DTX-3509 are not all of the values that exist inside of Teva using analytical techniques to measure these 15 standards, right?

A. I don't know for all of the values.

Q. In other words, you plotted some of the data, but you don't know whether there's additional data out there using different techniques to measure these 15 standards that aren't included in your analysis, right?

A. I plotted standards that are on the, on this table.

Q. But you didn't plot all of the values that are contained [1527] over the years inside of Teva for these 15 cop-1 markers, right?

A. I just plotted the values on this table.

Q. Why don't we take a look at DTX-1699. Take a look at the first page. And you see there is a, it's a letter from Scientific Polymer Products to Dr. Gad; you see that?

A. Yes.

Q. And Scientific Polymer Products is a third party vendor that will perform molecular weight analyses, right?

A. I'm not familiar with Scientific Polymer Products.

Q. And they're writing back to Dr. Gad and they're saying "Dear Dr. Gad, enclosed are revised results for the recently submitted MALLS samples." Do you see that?

A. I see it.

Q. And the date is August 7th, '95, correct?

A. Yes, it is.

Q. If you take a look at the 2nd page, we can blow up the first, the whole columns. See those are the same -- that column on the left includes the standards that you included on your graph in 431, right?

A. I have to compare the two tables.

Q. Take my word for it?

A. If you --

Q. If not, we'll look.

A. If you're representing that they're the same?

[1528]

Q. I am representing that. I'm representing -- there may be extra ones on this one, but this includes all the ones that you graphed. You see that.

A. Okay.

Q. Now, if you take a look at the ones that you plotted were the Mw values, that is the values in the first column.

And if could we get a split screen on that?

So in the far right column of the data that you looked at, that's Mw or the weight average used to obtain using MALLS, that's the first column that's on the left; you see that?

A. Well, that's a column determined using MALLS, column on the left simply says Mw.

Q. But in the first page it said that we used MALLS to run that standard, right?

A. It did mention MALLS in the letter.

Q. Okay. And if we take a look at the second column there, that's a whole another batch of data for these same cop-1 standards that is number average molecular weights, right?

A. Says Mn, yes.

Q. And you didn't include any of those values on your graph, right?

A. No, I didn't.

Q. Take a look at DTX-1642. If we could go to 1013041. You see here we have another table? Take a look at the left side. There is the listing of the cop-1 standards that you included [1529] on your graph, you see that? And I'll represent to you it includes the same 15. We could compare them if you like?

A. If you're going to represent that they're the same.

Q. And down the middle of the column there is the ultracentrifuge data; you see that?

A. It says -- yes, it says ultracentrifugation.

Q. That's the data that you included in your graph; that's the data that went into table, ends up in your graph?

A. I have to compare those values.

Q. Okay. Why don't we put them on split screen. If we could highlight ultracentrifugation column on the left. I'll represent to you that all the samples that you've included in the table on the left are on the table on the right, and the ultracentrifugation column. You see that?

A. I looked at the first three and four and they're the same yes.

Q. But take a look on the right. You see there are four more tables of information or molecular weight readings that existed inside Teva for those same copolymer-1 batches, right?

A. That table contains more values, yes.

Q. And those values were obtained using SEC columns, including the Superose 12 column, right?

A. It lists the Superose 12 column, and -- it lists the Superose column and the TSK column.

Q. And none of these values obtained using the Superose 12 [1530] column or the other column for the molecular weight of those samples was included in your graph, right?

A. The ultracentrifuge values were included.

Q. So the column down the middle was included, but the four set of the values on the left and the right of the center column was not?

A. They weren't in the table that I used.

Q. And so you didn't include it in your graph?

A. They were not.

Q. Now, sir, you'd agree with me that the general subject matter of the patents in suit is the production and measurement of low molecular weight to form copolymer-1 intended for the treatment of patients with multiple sclerosis; you agree with that, right?

A. Measurement of molecular weight.

Q. Well you would agree that the general subject matter of the patents in suit is the production and measurement of a low molecular weight form of copolymer-1 intended for the treatment of patients with Multiple sclerosis?

A. What do you mean by measurement?

Q. Well, let's take a look at your trial testimony in this case. Mr. James asked you last week, "Dr. Grant, what is the subject matter of the patents in suit? The general subject matter is the production and measurement of a low molecular weight form of copolymer-1. What is the low molecular weight [1531] form of copolymer-1 intended for? That's intended for the treatment of patients with Multiple sclerosis."

A. Yes, measurements of the molecular weight.

Q. For the purpose of treating patients with Multiple sclerosis?

A. That's what's product is used for.

Q. Yes. Now, as we've already established, the peptide markers, the synthetic polypeptides markers that Teva currently is using were not disclosed in any of the asserted patents, right?

A. That's right.

Q. And Teva considered these markers not only to be protected by the '938 patent, but also to be unique, a unique method of measuring the molecular weight of glatiramer acetate, right?

A. Would you repeat the question?

Q. Sure. Teva considers those markers not only to be protected by the '938 Gad patent, but also to be a unique method of measuring the molecular weight of glatiramer acetate, correct?

A. I don't know what Teva considers.

Q. Why don't we take a look at DTX-1738. You see that? DTX-1738 is a citizens petition that Teva filed with the FDA on September 26th, 2008; you see that?

A. It's dated September 26, 2008.

Q. If we go could go to 30009171?

[1532]

A. Okay.

Q. And you see that in this citizens petition to the FDA in 1998, Teva wrote, "In addition, Teva has developed a unique method of measuring molecular weight distribution based on the separation of glatiramer acetate polypeptides and calculates the

product's molecular weight distribution using a calibration curve generated from a set of well characterized proprietary polypeptide markers." You see that?

A. I see it.

Q. So Teva in the current method that it's using, which is not disclosed in the patents, considered that method of measuring molecular weight of copolymer-1 to be both unique and proprietary, correct?

MR. JAMES: Objection, your Honor. This is from a 2008 document. I'm not sure what the relevance is to Dr. Grant's testimony.

THE COURT: All right. Well, I've heard it now.

Okay, go ahead.

Q. And it's also true, isn't it, Dr. Grant, that given the huge number of variable patterns in the amino acid sequences of glatiramer acetate, even today those sequences have not been fully characterized; you agree with that?

THE COURT: That's just a question.

MR. JAMES: Objection.

THE COURT: Do you agree with that?

[1533]

A. They have not determined the sequences of molecules, yes.

Q. And as a result of that, it's taken Teva decades of studying glatiramer acetate and Copaxone to develop its testing procedures for the drug, including the method for molecular weight measurement to

ensure that there is consistency between each batch of the drug; isn't that true?

A. I don't agree.

Q. Why don't we take a look at DTX-1738 at page 12. Are you there, sir?

A. 1738, page 12?

Q. Yes, sir.

A. Okay.

Q. You see Teva wrote to the FDA in September of 2008 said "Given the complexity of the glatiramer acetate in Copaxone, including the huge perhaps incalculable number of variable patterns in its amino acid sequences, even the most state of art analytical techniques have not been able to fully characterize the pharmacologically active amino acid sequences within Copaxone's polypeptide mixture." You see that?

A. I see.

Q. As a result, Teva has spent decades studying --

MR. JAMES: Objection, your Honor. This really doesn't have anything to do with molecular weight.

THE COURT: No. The same thought occurred to me.

MR. ACKER: Well, this is the rigorous testing [1534] procedures are the measurement of molecular weight.

THE COURT: It doesn't say that.

MR. ACKER: That's what it is.

MR. JAMES: This document has to do with the products that are on the market, not the patents.

THE COURT: I don't -- look, you're telling me what it means, you're telling me what it means. What are we supposed with the Doctor?

MR. ACKER: I'm just going to ask the Doctor, if the Doctor is going to agree with that statement, that's fine. He's already stated he doesn't. If his mind is not going to change, that's great.

THE COURT: So we'll move on.

Q. All right, let me ask you few more questions about universal calibration, Doctor.

Your testimony hasn't changed from last week, you're still not an expert in universal calibration, right?

A. I haven't personally used universal calibration.

Q. And you're not an expert in universal calibration, right?

A. I've read a lot about universal calibration.

Q. And before becoming an expert in this case, as you said, you never used it, so all of your knowledge from universal calibration is based on reading the work of others, right?

A. Yes.

Q. And again we can agree that none of the patents in this [1535] case mention using universal calibration as a method to determine the molecular weight of copolymer-1, right?

A. That's right.

Q. And Teva itself during its years to characterize the molecular weight of copolymer-1 never used universal calibration, right?

A. I don't recall seeing that they used it.

Q. And you testified on direct that you believe copolymer-1 is a random coil, correct?

A. That's correct.

Q. And it's your belief that, and you understand that in order for universal calibration to work, the sample to be measured has to act like a random coil in solution, right?

A. No, I don't agree.

Q. But it is your testimony that co-polymer-1 is a random coil, is that correct?

A. That's correct.

Q. Why don't we take a look at DTX-1113.

MR. ACKER: A moment, your Honor?

Q. If we could go to page 312034.

And, Doctor, would your opinion change that copolymer-1 is, your belief that it is a random, acts randomly in solution, would it change if you knew that Teva had tested to determine in fact it is a non-random, it acts nonrandomly in solution?

[1536]

A. I don't think that's what it says.

Q. Well, let's read it. Relatively -- well, it's "A non-random distribution of helicity was found in a different fractions obtained from cop-1." Do you see that?

A. I see that.

Q. Then it reads, the components of cop-1 separated by reversed phase chromatography, contain different concentrations of amino acid residues supporting the non-random character of these components.

That was Teva's conclusion, correct?

A. I don't see where one follows from the other.

Q. You disagree with these findings of Teva?

A. I don't think there is enough information there to allow me to evaluate it.

MR. ACKER: That's all I have, your Honor. Thank you.

THE COURT: All right. We'll take a short break and then we'll have redirect.

10 minutes.

(Recess)

(In open court)

THE DEPUTY CLERK: All rise.

THE COURT: All right, be seated everybody -- all right, cross.

MR. JONES: Yes, your Honor. Sorry. Just give me a quick minute to get the binders out.

[1537]

CROSS EXAMINATION

BY MR. JONES:

MR. JONES: May I approach?

THE COURT: You may.

MR. JONES: Thank you.

Q. Good afternoon, Mr. Grant or Dr. Grant. I'm sorry.

A. Good afternoon.

Q. Sorry. Could I please have PTX-1 up, please. Let's start by looking at the '808 patent, if you will sir. And if I could go to column one of that patent, lines 32 through 34. You're familiar with this section of the '808 patent, are you not, sir?

A. Yes.

Q. And what I just wanted to make sure was that I wanted to have a point of clarification.

During your testimony in regard to the molar ranges, the molecular weight ranges that you determined from production of the Mylan empower data, you recall your testimony in that regard?

A. To some extent, yes.

Q. Right. You had the charts with the red X's indicating that you found that Mylan's product fit within certain molar ranges?

A. Yes.

Q. Right? And I think you said that that proved that all the claims in the patents in suit, the Mylan's product was covered [1538] by all the claims in the patents in suit; do you recall that?

MR. JAMES: Objection, your Honor. We didn't put a slide with Mylan's data and check marks.

THE COURT: I didn't think so either. I thought that was part of the objection.

MR. JAMES: That's right.

THE COURT: That you didn't have a slide.

MR. JAMES: Correct.

MR. JONES: There was not a slide, but there were check marks that you had gone through that the ratios, the two to 20, 75 percent between two and 20.

MR. JAMES: But this testimony is not from Mylan.

MR. JONES: All right. Let me just get real clear.

THE COURT: Okay.

Q. You are not testifying, based on what your analysis was, that Mylan's products fall within the 6:2:5:1 molar ratio, correct?

A. That's not what I was addressing.

Q. Exactly right. So you weren't saying that Mylan's products infringed, correct, based on your analysis?

A. I was -- based on my analysis, I was saying that Mylan's product infringed those claims which I was analyzing.

Q. Right. And among the claims that you were not analyzing was the approximately six to five to two to one molar ratio limitation, correct.

[1539]

A. I did not address that.

Q. Okay. So just so that we're clear, I just want a clear record that you are, based on your analysis alone, you aren't saying that Mylan's product infringes; there still needs to be further analysis, correct?

A. Actually I didn't say infringe. I didn't say infringe. I said met the limitations.

Q. Let me just go through your, just a couple of questions in regard to your particular qualifications and expertise, and one in particular, a couple, but I wanted to get clear.

Do you have any experience, sir, in gel chromatography, of random size distributions of synthetic polypeptides such as copolymer-1?

A. I have some experience in gel chromatography of disperse polypeptides.

Q. Random sized?

A. I didn't do anything to control the size.

Q. Were they random sized?

A. I think they were.

Q. And they were synthetic polypeptides?

A. Yes, they were.

Q. Okay. Have you worked with chemically synthesized polypeptides yourself?

A. Yes.

Q. What would you say as far as molecular weight, what [1540] polypeptide, chemically synthesized polypeptide is closest in your experience to in working with to copolymer-1?

A. You have to define what you're asking me to compare.

Q. Sure. I'm asking you to compare the body of work that you've done and the chemically synthesized polypeptides that you've worked with within that universe of work, I want you to tell me which of those chemically synthesized polypeptides is closest to molecular weight to copolymer-1?

A. I guess the best way I can answer that is that I've made polypeptides using chemical synthesis that were 40 to 50, sometimes 60 amino acids long.

Q. 60 amino acids long?

A. Yes.

Q. Did you publish anything on those?

A. No. This was made in our resource lab.

Q. At Washington university?

A. Yes.

Q. On that, do you have a size exclusion chromatographer at your research lab at University of Washington?

A. Washington University?

Q. Yes.

A. What do you mean by a size exclusion chromatographer?

Q. Do you have an SEC -- do you have the machinery necessary to conduct SEC molecular weight analysis?

A. Yes, I do.

[1541]

Q. Do you do that yourself?

A. I usually have a technician do it, but I have done it myself.

Q. In your definition of someone skilled in the art, if you could have that, I believe it's slide two, right. You would agree that the second part of your definition recognizes that a person of skill in this particular art is going to need to have access to and ability to consult with other scientists having related and/or complimentary knowledge, correct?

A. I didn't say they were going to need to. I said they would have access to.

Q. Would have access to. Because, well, you, yourself are not a toxicologist, correct?

A. That's correct.

Q. And you yourself are not a medical doctor, correct?

A. That's correct.

Q. So someone like you is going to need to be able to reach out to these, to specialists in these areas to get assistance to understand the art at issue, correct? The full range of the art covered in the patent?

A. Could you clarify what you mean the full range of the art?

Q. Well, you talked about the range of the art is advanced degree or equivalent in a chemical or biological discipline, significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides; correct?

[1542]

A. That's right.

Q. We're talking about an art as covered in the patent that involves a pharmaco kinetic substance that's used for the treatment of multiple sclerosis, correct?

A. Yes.

Q. So you would simply agree, sir, that a single person would be an extraordinary person who would have high level of skill in all the disciplines necessary to fully understand and to fully implement inventions in this field of art, correct?

A. You're asking me if there was a single person who was a medical doctor, who was an expert in toxicology, and an expert in all those other things listed there would be amazing person?

Q. Can you name one?

A. No.

Q. So, of course -- so it's a simple question. For your definition --

THE COURT: I think you've asked it and he's answered it.

MR. JONES: Exactly right.

Q. All right. So it simply makes sense that a person of skill in the art here is going to be a person who doesn't have to have expertise in all these sub areas, but would reasonably rely on the expertise of others. That's all I'm asking.

A. I think that's what it says.

Q. All right. Now I wanted to -- I'm going to be fairly -- [1543] try to be targeted with your cross. You've been up a long day.

Let me talk about teaching away, and in particular you referred to an abstract that was published in 1974 in which some of the inventors talked about a copolymer-1 which they recommended to be 15 kilodaltons or above, correct; you remember that?

A. To 15 or was it 17?

Q. You don't remember?

A. I think it was 17.

Q. 17. So you were thinking that in '74 the inventors were saying, don't try copolymer-1 to treat multiple sclerosis with anything less than 17 kilodaltons, right?

A. They said in their experience based on that abstract, that they found no activity below that level.

Q. All right. Could we go to PTX-31. And you recognize this as the Bornstein 1987 study, correct?

A. I don't think I have 31.

Q. Look in your binder, sir?

A. In my binder?

Q. I believe it was in your direct binder. If it was not, I'll get you a copy.

THE COURT: We could use the screen, Doctor.

A. Yes, I have it.

Q. All right. I'm simply going to point out this is an article from 1987. You can see that from the top right [1544] lengend, correct?

A. Yes.

Q. It reports on the study that was conducted even earlier than 1987, correct?

A. Yes, I think so.

Q. Let's go to the first paragraph of the Bornstein study -- nope, not in the abstract. There we go.

So despite the warning that you recall seeing of not trying copolymer-1 below 17,000, you'd agree that Dr. Bornstein tested copolymer-1 at 14,000 daltons, correct?

A. That's what's listed there.

Q. Right. And I know that you're not a toxicologist, but I know you've read this study, you would agree that he found the 14,000 dalton molecular weight copolymer-1, nontoxic, correct?

A. I, frankly, don't recall. It's been a long time since I read this article.

Q. All right. Certainly found it was effective in treating multiple sclerosis, correct?

Doctor, if you haven't read the study, that's fine.

It will speak for itself.

A. I've read the study. It's been a long time ago, and I just don't recall the details.

Q. Let's focus on the '808 patent.

Now, you recognize, as the Court found in its claim construction order, that copolymer-1 is a complex non-uniform [1545] mixture of molecules of varying weights, correct?

A. Varying sizes and sequences.

Q. All right. And as such, the most precise way of describing the molecular weight of copolymer-1 is a complete molecular weight distribution; you'd agree with that, right?

A. Yes.

Q. And is it your belief that the most precise way of describing the molecular weight of copolymer-1 is a complete molecular weight distribution is because copolymer-1 is polydisperse?

A. Yes.

Q. So, for example, my understanding is that certain proteins, single chain proteins, you can identify their molecular weight with simply a single value, correct?

A. Do you mean that all molecules have the same molecular weight?

(Continued on next page)

[1546]

Q. Right.

A. If it was a pure protein, yes.

Q. Exactly right. You wouldn't need a wave distribution to show the molecular weight of that type of protein, correct?

A. That's right.

Q. But copolymer-1 is different, right?

A. Yes.

Q. And we have some example of molecular weight distributions or profiles in the '808 patent itself, correct?

A. There are a couple of figures, yes.

Q. Right. Let's go to column 1, lines 55 through 60 of the '808 patent.

A. What's the number for it?

Q. Oh, PTX, I believe it's PTX 1.

A. Okay.

Q. All right? And again, you can look at the screen if you want, but however you want to do this, I'm simply bringing out to you part of the '808 patent and this is the brief description of the drawings, right?

A. Yes.

Q. This appearance in a common specification, that's specifications common to all the patents in suit, correct?

A. I think so.

Q. The patentees explain that figure one displays the molecular weight distribution of three batches of copolymer-1 [1547] showing the proportion of species with molecular weight above 40 KDa, correct?

A. That's what it says.

Q. Let's take a look at figure 1. Figure 1 is depicting average molecular weight, correct?

A. That's what it says.

Q. And it's depicting two batches which are virtually identical at the claimed range or within the claimed range of 7.7 kilodaltons, right?

A. Yes.

Q. You recall that the '808 patent claimed a range of 5 to 9 kilodaltons, correct?

A. Yes.

Q. So the 7.7 curves, that's what a copolymer-1 within the claimed range looks like, right?

A. That's the curve that's shown there.

Q. Right? And the 12.0 curve, that's a curve that would fall sort of in the prior art range, correct, of copolymer-1?

Outside of the claimed 5 to 9 range?

A. Well, it's outside of the 5 to 9, but I don't think the prior art mentions 12.

Q. Well, we had a discussion about this, right, and you discussed with counsel on cross-examination the fact that Teva told the Patent Office that the '550 patent taught a copolymer-1 to 10 kilodaltons, correct?

[1548]

A. No, that's not correct.

Q. Teva didn't say that to the Patent Office?

A. Well, they said that in their prosecution, yes.

Q. How many times, do you know how many times they said it?

A. I don't know the number of times, no.

Q. I'll represent to you three times to the Patent Office, three separate times they told the Patent Office that.

A. All right.

MR. JAMES: Objection, your Honor. I'm not sure that's accurate.

THE COURT: Sustained.

Q. I will ask you to do this, sir. Let's assume that Teva was accurate when it made its representation to the Patent Office, that the '550 taught down to 10 kilodaltons, all right?

A. You're asking me to assume that.

Q. Yes, assume that Teva was accurate. Okay?

A. Mm-hmm.

Q. So given that definition you'd agree that the 12 falls within the prior art range for copolymer-1, right?

A. I believe 12 is above 10.

Q. Okay, sir. You would agree that the curve for the prior art range, 12 copolymer-1 overlaps with the curve for the claimed 7.7 range, correct?

A. By overlapping you mean there are common areas?

Q. Yes, exactly. Right.

[1549]

A. Yes.

Q. I'll see if I can use this with some steadiness. This is the place of overlap, right?

A. Yes.

Q. So what we're describing here, what I'm depicting here is the place where the prior art

copolymer-1 and the claimed copolymer-1 share identical molecular weight distribution, correct?

A. There is a similar distribution there.

Q. Now, if you could do some teaching, I'm placing the pointer where I believe you would say Mp is, is that right?

A. It's about there.

Q. Right about the top of that curve, that's where the 12 is of molecular weight, correct?

A. About.

Q. And that's about 7.7, correct?

A. About.

Q. And Mw, where would I find that; over here, about? Weight average?

A. Weight average; weight average would be higher.

Q. Okay, here?

A. No.

Q. Where? Where would I put it?

A. Somewhere on the ascending slope.

Q. Right over here?

[1550]

A. Well, I mean in that area. I can't say precisely where.

Q. So Mw is going to be in this area, right?

A. Possibly.

Q. And Mw for the 12 curve would be about here, correct?

A. Possibly.

Q. And MP will be up here, though, for the 12 curve, right?

A. Yes.

Q. All right. And we're going to see that Mw always has a higher value than Mp, is that correct?

A. In general it does for curves of this type.

Q. Do you know of an instance where -- do you know of any instance of copolymer-1 that has been measured where the Mw was not higher than the Mp?

A. I don't recall seeing one.

Q. Now, do you agree that what we're looking at are curves where the difference in the molecular weights, the average molecular weight is a little over 4 KDa, correct?

A. Yes.

Q. Right? So, and it's true that if we were to move the curve back, that is, if the 12 were in fact an 11 or a 10 we'd tend to see even greater, greater overlap between the claimed range and the range of something outside the claims, correct?

A. If you're going to produce more overlap, you would see more overlap.

Q. Well, I'm not just producing more overlap, I'm saying if my [1551] weights are closer, if instead of comparing 7.7 to 12 I was comparing 7.7 to 12, you'd

expect to see even more overlap, more identity between the molecular weight distributions of the two species of copolymer-1, correct?

A. I suppose that's possible.

Q. Is it possible or is that what you'd expect to see?

A. I'm not quite sure what you're trying to show.

Q. All right, well, maybe we can -- let me ask you this: You talked a lot about the state of the art, the state of skill in the art as of 1994, correct?

A. I did.

Q. And in your view the state of the art or the folks who were of skill in the art in 1994, they would know very well how to use size exclusion chromatography to analyze a copolymer-1, correct?

A. A person skilled in the art, yes.

Q. They would in fact, and they'd know how to make copolymer-1 because they'd be able to read the 1971 Teitelbaum paper and the '550 patent which enabled a person of skill to make copolymer-1, yes?

A. They could make copolymer-1, yes.

Q. So a person of skill in the art in 1994 had the analytic tool, size exclusion chromatography, and the recipe for copolymer-1, so that they could determine a molecular weight distribution for copolymer-1, correct?

[1552]

A. Yes.

Q. Now, could I have 1704R, please, DTX 1704R, which I believe was previously admitted during the testimony I believe of Dr. Zeiger. And you were here for that testimony, right, sir?

A. Which binder is it in?

Q. I think it's in my binder, the smaller binder, and we're only going to use the redacted version.

A. I have it.

Q. Okay. So, you recall, don't you, that Dr. Zeigler talked about 1704 in his testimony?

A. Yes.

Q. And you've had a chance to look at 1704, right?

A. Yes.

Q. You know that 1704 is a document prepared by Dr. Gad, right?

A. Yes.

Q. And I know that you at least understand that Dr. Gad had a fair degree of experience personally with copolymer-1, correct?

A. I understand that he's worked on it.

Q. So even though he may not fit your definition of a person of ordinary skill in the art he had worked for multiple years on copolymer-1, correct?

A. He worked for several years, yes.

Q. Now, we've seen this study. You'd agree that what Dr. Gad is doing here is he's establishing an analytical link between [1553] early clinical batches of copolymer-1 and current production batches of copolymer-1?

A. That's what the title says.

Q. And if we go to the first page, you'd see in the introduction, if we have that first paragraph, and actually the next one as well. This simply identifies exactly what Dr. Gad is doing. He's taking the trial BR-1 which refers to the actual trial that Dr. Bornstein conducted, correct?

A. Yes.

Q. And what he's done is he's taken actual samples, actual copolymer-1 samples from the trial that Dr. Bornstein conducted and what he's doing is he's comparing them to -- you see that trial was performed, a drug substance manufactured by Teva, so he's comparing the three Bornstein products with a product prepared by Teva, correct?

A. That's what it appears.

Q. Right. Now, let's go to table -- actually, let's go to table 1 of the report. You understand that one of the analyses that Dr. Gad conducted was he took what had been recorded as the average molecular weight by ultracentrifugation, which we see in the far right column, correct?

A. I see that.

Q. So these are the average molecular weight by ultracentrifugation that had been, that characterized the copolymer-1 used in the Bornstein study, right?

[1554]

A. It characterized those three samples there, yes.

Q. And so we see that WIS 320 had an ultracentrifugation molecular weight of 11,000 daltons, right?

A. That's what it says.

Q. 340 has 15,500, right?

A. Yes.

Q. And WIS 400 has 16, correct?

A. That's what it says.

Q. So, again, Dr. Bornstein in his study was using copolymer-1 at least as measured by ultracentrifugation as low as 11,000 daltons, correct?

A. That's what the number says, yes.

Q. And then what Dr. Gad did was he then reanalyzed those samples and obtained their peak values, right? And we see that in the column right next to the identification of the samples, average molecular weight. Right?

A. I see it says average molecular weight, but I'm not sure what it refers to.

Q. Okay. Would you please highlight the information under table 1? Do you see that? There you go. Thank you. Go ahead and highlight that table. You would agree, sir, that Dr. Gad explains that table 1, molecular weight distribution of three BR-1 batches as determined by gel permeation chromatography in comparison to the original determination by ultracentrifugation, right?

[1555]

A. That's what it says.

Q. So again, the column right next to the sample identifiers, it says average molecular weight that reflects the gel permeation chromatography molecular weight, right?

A. That appears to be the molecular weight that was determined by gel chromatography, correct.

Q. And that would reflect a peak, correct?

A. It doesn't say it's a peak average.

Q. But a person of skill in the art would understand it to be peak, correct, sir?

A. Yes.

Q. And, just as you told us before, the Mw is larger than the Mp, correct, for all the samples, correct? Mw would be the average molecular weight by ultracentrifugation, correct?

A. Well, no. I mean, you can get different average molecular weights from ultracentrifugation.

Q. Do you have a reason to believe that the average molecular weight by ultracentrifugation is not Mw?

A. I don't have any indication that it's not.

Q. What else would it be?

A. It could be Mz.

Q. But you would agree that reflects peak values, correct?

A. If we're interpreting this table correctly, that's what it appears to be, yes.

Q. Peak values that show that the molecular weights go from [1556] 1550 to 13450 for the 340 sample, right? And from 1600 to 14350, correct?

A. Those are the values listed there, yes.

Q. It compares to a Teva product in the claimed range of 5 to 9 kilodaltons, right? The Teva product has a 7150 dalton range? Molecular weight?

A. The Teva 03494 is listed as 7150.

Q. And that falls within the range of 5 to 9, correct?

A. That's within the range of 5,000 to 9,000.

Q. All right. Let's go to the conclusion section, keeping this information in mind. So if you would go to TEV 3004355. There you go, the first paragraph. You've got three conclusions I want to talk to you about. If you highlight the last sentence.

According to Dr. Gad, who had personal experience working with copolymer-1, the reanalysis for average molecular weight revealed that the three BR-1 batches revealed results very similar to those originally determined by ultracentrifugation, correct?

A. That's what it says.

Q. That's what Dr. Gad's conclusion was?

A. That's what it says.

Q. So according to Dr. Gad the molecular weight varied by as much as 2,000 daltons, those weights were very similar correct?

Would you like to go back and see the table --

[1557]

A. He says they're similar.

Q. So a difference of 2,000 daltons, those molecular weights are still very similar to Dr. Gad's, correct?

A. Within 50,000 daltons.

Q. Which you would characterize as very similar, correct, Doctor?

A. Well, I would characterize it as being within 50,000 daltons.

Q. Let's go to the next page. Please highlight the first paragraph. Here Dr. Gad concludes that regardless of the average molecular weight a substantial overlap between the molecular weight distribution profiles of all the BR-1 batches and those of the reference standard was observed. Do you see that?

A. I see that.

Q. Substantial overlap. Now, you recall that the reference standard was 7100 daltons, correct about that?

A. Yes.

Q. And you recall that that reference standard was compared to standards that were as high as -- let's go to table 114380, correct? So what Dr. Gad concluded was the molecular weight distribution between a molecular weight of 14350 exhibited substantial overlap between the referenced standard of 7,150, correct?

A. I believe that's what Dr. Gad said.

[1558]

Q. You disagree with Dr. Gad?

A. No, if I read it correctly, that's what he said.

Q. In fact, let's go to the table listing, I believe it is 3, the molecular weight distribution, so we can see something. Keep going next. Next page? Next? Back a page. Back a page? That's it? We've redacted this. We won't be able to show this.

Would you agree that the molecular weights became closer to the reference standard, that is, there was a reference you can see -- that's actually the next one -- as the molecular weights become closer to the reference standard the amount of overlap increased, you'd agree with that, correct?

A. I didn't see numbers that said that.

Q. Okay. Here we go. I appreciate your patience. See the overlap percent of the mass column?

A. I see a column.

Q. Right, and you'll recall that the 320 sample, that has a molecular weight of 10350, right?

A. I don't remember the numbers.

Q. Well, I'll represent to you that WIS 320 had a molecular weight of 10350, correct?

A. Okay.

Q. And when compared to the reference standard of 7150, Dr. Gad reports an overlap of the mass of 83 percent, correct?

A. That's what it says.

[1559]

Q. And then the WIS 400, that was the largest of the samples, that was a 14350 peak, when compared to the reference, molecular weight distribution of the reference standard of 7150, he found a 68.6 percent overlap, correct?

A. That's what it says.

Q. Right. So again, we see that as the molecular weights become closer at their peaks, the amount of overlap of their molecular weight distribution increases, right?

A. That's what the numbers seem to indicate.

Q. Do you know of any experimental tests that would show otherwise involving copolymer-1, sir? Have you personally seen any experiment, any data analysis suggesting that the phenomenon we're seeing here is not carried out across the board with copolymer-1?

A. I don't understand your question.

Q. Well, all I'm trying to get you to -- what we're trying to understand here is as the molecular weight of a reference and another sample become closer, the overlap increases.

A. That seems to be the case for these three samples.

Q. And that's why I wanted to just check to see if I might have missed something. Are you aware of any other analysis where as the molecular weights grew closer the overlap did not in fact increase?

A. I'm not aware of all analyses, I really don't know.

Q. I didn't ask you -- I just asked if you knew of one where [1560] you didn't see this.

A. Where the molecular weights became closer and the overlaps did not increase?

Q. Right, with copolymer-1.

A. I don't recall seeing much of that at all that addresses that.

Q. I didn't ask you how much you saw. I asked you if you could remember a single study showing that as the molecular weight of the two comparers as they get closer together, did you see anywhere the molecular weight distributions decreased?

A. I don't recall.

Q. If we could go back to the conclusions. Can we have the last paragraph highlighted? Dr. Gad reports that the most relevant biological activity testing, blocking of EAE in mice, again, EAE testing, that's something a person of skill in the art in 1994 would know how to do, right?

A. Well, a person who is skilled in that aspect.

Q. In fact we saw EAE analysis back in 1971 with the Weizmann Institute?

A. I would agree that a person involved in EAE would be able to do EAE.

Q. So the most relevant biological activity testing, blocking of EAE in mice again revealed that all batches are similarly highly active. Do you see that?

A. I see that.

[1561]

Q. In fact, if we can go to the actual results -- before we get there, that's fine, let's go to the actual results, because it said they were similar but let's look at what was actually reported at table 6.2, EAE blocking, 6.2 on page YED 5005. Thank you.

A. I see it.

Q. In fact, what we see is that despite the range of 6,000 daltons between WIS 400 and the reference standard, we're seeing that all the samples show 100 percent EAE blocking, correct?

A. These three samples show that.

Q. Right. Including that sample of 10,350, correct?

A. Yes, that's WIS 320.

Q. Now, I'm going to ask you, Doctor, based on what you've seen and I know you haven't seen everything, but just based on what you have seen, what would you expect to see as the percentage of overlap in the molecular weight distribution between a copolymer-1 with a peak of 9 kilodaltons and a copolymer-1 with a peak of 10 kilodaltons?

A. In regard to what?

Q. In regard to the overlap of molecular weight distribution.

A. There would be some overlap.

Q. Would you care to quantify that for me? Can you estimate a quantity?

A. I'm sorry, I don't understand what you're asking.

[1562]

Q. Let's go to table 2. The molecular weight distribution table.

A. Okay.

Q. All right? We see a molecular weight overlap of 83 percent when comparing a sample of 10,350 to a sample of 7,150, correct? Correct?

A. Yes, we do.

Q. That's a difference of 3,000 daltons?

A. That's what it says in this table.

Q. If the difference weren't 3,000 daltons but instead were 1,000 daltons you would expect to see an even greater overlap of the percent of mass, correct?

A. It's hard to answer that without seeing the data.

Q. And it's the molecular weight distribution which determines the characteristics of the copolymer-1 sample, correct?

A. Depends what the distribution actually is.

MR. JONES: Nothing further.

THE COURT: Any redirect?

MR. JAMES: I do, your Honor. I just have a few questions.

REDIRECT EXAMINATION

BY MR. JAMES:

Q. Mr. Int-Hout, can you put up Plaintiff's Trial Exhibit 1, please? If you could put figure 1 on the

screen. Dr. Grant, you remember counsel asking you a few questions about figure 1

[1563]

of the patents and the distributions shown there?

A. Yes.

Q. Figure 1 of the of patent, is that something that was available to a person of skill in the art of these patents prior to their filing?

A. No.

Q. Let's look at Defendant's trial Exhibit 1704.

A. Okay, which --

Q. This is the document that counsel was just asking you about that was authored by Dr. Gad. And you see this document, do you see what it says in the lower left-hand corner of the document, Dr. Grant? Do you have it there in your binder?

A. I haven't found it yet. Just hold on one second, please.

Q. You can see it on the screen?

A. Okay, the lower left-hand corner.

Q. Yes, the legend there?

A. External counsel only.

Q. Yes. Do you see the date of this document?

A. July 18, 1995.

Q. That's right. Was this material that you were just questioned on, was this material available to a person of skill in the art prior to May 24, 1994?

MR. JONES: Objection. Foundation.

Q. Was this document available?

THE COURT: The document's -- okay.

[1564]

A. No, it was not.

Q. Let's look at table -- I'm sorry --table 1 on page 3004347.

Counsel, if you could blow that table up, please. Counsel asked you some questions about these molecular weights. The average molecular weight column there, the second column, Dr. Grant?

A. Yes.

Q. And he asked you questions about the peak molecular weight of 7150 compared to the others?

A. Yes.

Q. Is there any overlap in the peak molecular weight of any of those batches?

A. Those batches compared to 03494?

Q. Yes.

A. No, there's not.

Q. All right, let's look at Defendant's Trial Exhibit 3510. I think that would have been in the binder that Mr. Acker provided you. Do you have that? Do you recall being asked questions about this document, Dr. Grant?

A. Yes, I do.

Q. Let's look at a few of the things that are found here. First I think he directed you on the first page to heading C? Do you see that?

A. Yes.

Q. Heading C talks about globular protein markers?

[1565]

A. Yes.

Q. Could you read the next sentence, the first sentence of the next paragraph into the record, please?

A. Starting with, "As could"?

Q. Yes.

A. "As could be expected from the explanations in item A, the apparent molecular weight of copolymer-1 was four to five times higher than that obtained by viscosity or ultracentrifugation, Table 1, Figures 1 and 2."

Q. When it says "as could be expected," Dr. Grant, what does that suggest to you?

MR. ACKER: Objection. Calls for speculation.

THE COURT: It would seem to.

Q. I think the question was -- well, let me ask a different question. What do you understand that to mean?

MR. ACKER: Same objection, your Honor. Just couched a different way. He's asking what the writer thought.

THE COURT: I don't care about anybody's state of mind here. What can you tell me, do you know anything about --

MR. JAMES: I'll ask a different question, your Honor.

THE COURT: Okay. You'll be better at it than me, but ask the right question and you can get the answer.

Q. I think, Dr. Grant, in 1994 would a person of skill in the art have expected a protein standard, globular protein standard to have the same hydrodynamic characteristics as copolymer-1?

[1566]

A. In my opinion they would not.

Q. And does this sentence support that opinion?

A. Yes, it does.

Q. In what way?

A. Well, it says that the apparent molecular weight using globular proteins is four to five times higher than from viscosity or ultracentrifugation. And that indicates that that erroneous result is because the size to molecular weight relationship is different in the standards in the sample.

Q. Let's look at the next page, 1116322 heading D, PEG, polyethylene glycol markers. Do you see that?

A. Yes.

Q. Counsel asked you some questions about that passage?

A. Yes.

Q. Now, in 1994, Dr. Grant, would a person of skill in the art have expected polyethylene glycol standards to have the same hydrodynamic characteristics as copolymer-1 molecules?

A. No.

Q. And if you read, look at the sentence that begins, "As could be expected from the smaller side groups in the PEG, i.e., OH in respect to the side chains in the peptides," does that support your opinion about the expectation in 1994?

A. Yes.

Q. In what way?

A. Well, it supports my opinion in that a person skilled in [1567] the art wouldn't expect these standards to have the same size to molecular relationship because they were not the same type of molecule.

Q. Dr. Grant, if you look at part G on page 1116323, please.

A. Okay.

Q. I believe you testified earlier that in 1994 a person of skill in the art would have had access to broad molecular weight standards for copolymer-1, namely, self standards, right?

A. Yes, that's right.

Q. And if you look at the sentence, the second sentence in part G, it says, "Markers or standards with broad molecular weight distribution are well known in GPC." Do you see that?

A. Yes, I do.

Q. Does that support your opinion, Dr. Grant?

A. Yes, it does.

Q. Could you explain that?

A. Well, it says that they were well known in GPC, which indicates to me that they had been used previously, probably on a large number of different occasions, and markers or standards with broad molecular weight are exactly what self standards are.

Q. Let's look at Defendant's trial Exhibit 1706. Do you have that? That's also in the binder Mr. Acker provided you.

A. Okay.

[1568]

Q. And you were asked some questions about SEC MALLS having to do with this document, correct?

A. Yes.

Q. And in particular you were asked some questions about the page TEV 3004390, right?

A. Yes.

Q. Now, SEC MALLS is not a size exclusion column that has been calibrated, correct?

A. That's correct.

Q. Could you explain that?

A. With SEC MALLS it uses an absolute technique called multi angle laser light scattering and even though you use a size exclusion column it's not necessary to calibrate it with standards because the light scattering basically does the job for you.

Q. Dr. Grant, do you understand this document to have any relevance to a peak molecular weight determined on an appropriately calibrated suitable gel filtration column?

A. No, I don't. It has something completely different.

Q. And what is that thing that's completely different about it?

A. It's not a calibrated column.

Q. Let's look at Defendant's trial Exhibit 1762, please.

A. Okay.

Q. And I'd like you to turn to page 3017846.

[1569]

A. Okay.

Q. Counsel asked you some questions about heading 3.

A. Yes.

Q. Correct? And there it talks about some alternative molecular weight calibration standards, correct?

A. That's right.

Q. Now, from what you've -- your review of the Teva documents, Dr. Grant, this document is dated May 4, 1988. Was Teva already using copolymer-1 self standards by that time, by May 4, 1988?

A. Yes, they were.

Q. You were asked some questions about a document that says that the technique for measuring the molecular weight of copolymer-1 should be explicitly stated. Do you recall that?

A. I do.

Q. And do the patents in suit, Dr. Grant, do they explicitly state the technique that should be used to determine the molecular weight of copolymer-1?

A. Yes, they explicitly state that it's size exclusion chromatography.

Q. I believe you were also asked some questions about vapor phase osmometry, do you recall that?

A. Yes.

Q. And I believe you testified earlier that you thought osmometry could be used as an absolute technique for the [1570] measurement of molecular weight for copolymer-1, right?

A. That's correct.

Q. Now, are there different types of osmometry?

A. Yes, there are.

Q. And is there one that would be more appropriate for copolymer-1 than the other?

A. Yes, it's memory osmometry.

Q. So does the text about vapor phase osmometry, does that have anything to do with the technique that you were referring to earlier in the day for measuring the molecular weight of copolymer-1?

A. No, it doesn't. It's completely different.

Q. Could you turn in your binder to Defendant's trial exhibit 3507?

A. Okay.

Q. And you were asked some questions by counsel about this document, correct?

A. I think so.

Q. You can take a moment to look through it, Dr. Grant, but this is a document in which Teva submitted new SEC calibration markers to the FDA, is that right?

A. Yes, I recognize it.

Q. And could you look at page 213933?

A. Okay.

Q. And counsel had you read --if you could pull up that [1571] paragraph, Mr. Int-Hout -- you could put it on the private screen, please. Could you pull up the paragraph on 213933? Maybe we're not going to be able to pull it up.

Dr. Grant, you were asked about this, the sentence that begins with "the molecular weights"?

A. There it is. Yes. Yes.

Q. And there it talks about some differences between the calibration curves that were created by these standards?

A. Yes.

Q. Counsel didn't ask you to read the next sentence?

A. No.

Q. Could you read that sentence into the record, please?

A. "This relatively small difference supports the claim that these markers can replace the currently used glatiramer acetate molecular weight markers without significant change in reported molecular weight values compared to previous years."

Q. And in fact, did the FDA allow Teva to make this substitution of the peptide standards for the copolymer-1 markers?

A. Yes, they did.

Q. And did the FDA require any change in the specification for Copaxone?

A. No.

Q. Let's look at the next page, 213935, please, section 5.2, consistency in reported values cross validation. Do you see [1572] that?

A. Yes, I do.

Q. And this discusses the testing of six batches of glatiramer acetate and the results are provided in table 5, right?

A. That's correct.

Q. If you could read the last sentence into the record of the paragraph on 213935, please?

A. "The difference in the results was typically less than 10 percent, table 5."

Q. And what does that indicate to you about the similarity between the copolymer-1 markers that

Teva used and the peptide standards that it was introducing to the FDA?

A. It indicates to me that they produced very similar results, certainly within the expected variation of the technique itself.

Q. Dr. Grant, could you turn in Mr. Acker's binder to PTX 431, please. Mr. Int-Haut, you could put that on the screen.

A. Okay.

Q. This was a graph that you created during the course of this litigation from a set of data in a Teva document, correct?

A. Yes.

Q. And Mr. Acker asked you some questions about that document today, correct?

A. Yes.

Q. Why did you create this graph, Dr. Grant?

[1573]

A. It was in response to an expert report that was filed by one of their experts.

Q. Which expert was that?

A. Dr. Scandella.

Q. Dr. Scandella relied on these data originally?

A. Yes, he did.

Q. And what was his point in relying on these data?

A. What he did was he compared the lowest value to the highest value and said look, it varies by something like 24 percent.

Q. And when you plot the data, Dr. Grant, will they result in a calibration curve that will give you a different peak molecular weight?

A. No, it will not, because the variation is not systematic.

MR. JAMES: I have nothing further.

MR. ACKER: Just a few, your Honor, if I might.

THE COURT: Sure.

RECROSS EXAMINATION

BY MR. ACKER:

Q. Dr. Grant, MALLS was the method that Teva was using between -- after 1992 until 1998 to measure the cop-1 self standards, correct?

A. They used MALLS sometime during that period, yes.

Q. So when you said MALLS had nothing to do with SEC that wasn't entirely accurate because Teva was using MALLS to measure the molecular weight of their self standards, right?

[1574]

Grant recross

A. I said it had nothing to do with appropriately calibrated SEC column.

Q. But it did have something to do at Teva about measuring the molecular weight of their cop-1 self standards, right?

A. I believe they used it to measure molecular weight, yes.

Q. Mr. James asked you whether the way to calibrate the column was disclosed in the patent. All the patent says is you need a suitably calibrated SEC or Superose 12 column, right?

A. The patent says you should use a Superose -- suggests using a size exclusion chromatography column and a Superose 12 is in parenthesis and suggests it should be calibrated.

Q. But it doesn't tell you how to calibrate the column, right?

A. It does not.

Q. And it doesn't tell you the technique you should use to calibrate the column, right?

A. As far as --

Q. It doesn't say use self standards, right?

A. No, it does not.

Q. And it doesn't say that if you use self standards what analytical method you should use to measure the molecular weight of those self standards, doesn't include that, right?

A. It doesn't say that.

Q. Let me ask you about the chart, or let me go back to 3507. If we could go to the table 3B on 213934.

A. Okay.

[1575]

Q. Now, there's a list of markers there and on the left column is the retention time, that's the time that that particular marker is coming out of the column, correct?

A. Table 3B?

Q. Yes, sir.

A. It's a relative retention time.

Q. Yes, and if you see there's one column Mw1 that is the results that you get if you use the old cop-1 self standards, right?

A. That's what the glatiramer acetate refers to, yes, I think so.

Q. And next to it for Mw2 you get the results you get if you use the new specific polypeptide standards, right?

A. Those are referred to as the TV standards, yes.

Q. If you go down to the retention time row of .62, do you see that?

A. I see it.

Q. And if you were to use the old standards, you would get a molecular weight above 10,000 kilodaltons, right?

A. If there was a peak at that position.

Q. And if you use the new specific polypeptides, you would get a molecular weight reading below 10,000 kilodaltons, right?

A. If there was a peak at that position.

MR. ACKER: That's all I have, your Honor.

MR. JONES: No questions for Mylan, your Honor.

* * *

[PTX 198: Momenta Analytical Method Development Report]

1.0 Table of Contents

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2.0 Revision History

Rev #	Date	Section(s)	Description of Revision	Reason for Revision
00	See front page	NA	NA	Initial Document

3.0 Objective

The objective of this report is to document the effort to develop and implement methods able to characterize the molar mass distribution of Glatiramer acetate and Glatiramer acetate Injection.

4.0 Scope

This report covers the development of the methods to characterize the molar mass distribution of Glatiramer acetate and Glatiramer acetate Injection. These methods were used to support Process Development. The same methods are also applied to the release and stability testing of Glatiramer acetate and Glatiramer acetate Injection.

5.0 References

See Footnotes.

6.0 Initial Development work

6.1 Introduction

The first approach used to measure the number and weight average molar masses of Glatiramer acetate samples was Size Exclusion Chromatography (SEC) coupled with a Multi Angle Light Scattering detector (MALS) and a Refractive Index detector (RI). This system set-up is based on the Rayleigh scattering law[26],[27] and allows the "absolute" characterization of the molar mass distribution

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[26] "Light Scattering from Polymer Solutions", Chapter 6, M.B. Huglin, Academic Press, London and New York (1972)

[27] "Light Scattering and the absolute characterization of macromolecules", Wyatt P.J., *Analytica Chimica Acta*, 272, 1-40 (1993)

without specific standards, providing the refractive increment (dn/dc) of the macromolecular distribution in the mobile phase is known. The SEC-MALS is a technique widely used at Momenta, and it was a natural and practical first option for analysis of Glatiramer acetate. To implement the method, the dn/dc value for Glatiramer acetate needed to be measured.

6.2 First dn/dc measurement

The first dn/dc measurement was done in June 2005 on a Reference Listed Drug (RLD) material in which mannitol had been removed by a bag-dialyzis process at Momenta. Very little amount of material was available to determine the dn/dc. A value of 0.153 mL/g was obtained. The detail of the experiment is reported in Attachment 1.

0,153 mL/g dn/dc value did not result in molar masses consistent with the label of the Reference Listed Drug. However, even if the accuracy was in doubt, the SEC-MALS method was a valuable comparative tool to support the Process Development effort to develop and optimize the Glatiramer acetate process. The method described in Section 6.3 has been extensively used for that purpose. Multiple lots of RLD were measured, leading to the establishment of equivalence windows for the number average molar mass, the weight average molar mass, the molar mass at the apex and the polydispersity. The equivalence windows were used to compare Glatiramer acetate produced for the Momenta program relative to the RLD.

6.3 SEC-MALS method parameters

The initial parameters for the SEC-MALS method are shown in Table 1 below.

Table 1: Initial Method Parameters

Chromatographic System:	1-IPLC system equipped with isocratic pump and on-line degasser Wyatt miniDAWN® Tristar™ Multi Angle Light Scattering (MALS) detector. Optilab rEX interferometric refractometer (RID), or other suitable Wyatt RID
Mobile Phase:	0.2 M Sodium Sulfate with 0.05% Sodium Azide buffer pH 5.5 ±0.1
Flow Rate:	0.5 mL/min
Columns:	Tosoh SW_{XL} Guard column (6mm x 40 mm), Tosoh TSKgel $G3000SW_{XL}$ (7.8 mm x 300 mm), Tosoh TSKgel $G2000SW_{XL}$ (7.8 mm x 300 mm),
Column Temperature:	Ambient
Autosampler Temperature:	4°C or ambient
Injector Volume:	100 µl
Run Time:	60.0 min
Detection:	MALS FRID (PDA optional)
RID Temperature:	25.0°C

After the first dn/dc measurement, the pH of the mobile phase was decreased to be more compatible with long term use of the column. The dn/dc was not

re-measured immediately after that method modification.

7.0 Further development of the method

7.1 Re-measurement of the dn/dc of Glatiramer acetate

The experimental procedure to accurately and reproducibly measure the dn/dc of a macromolecule in solution was extensively investigated and optimized for another Momenta program (See Technical Report DEV-06-0018, Specific Refractive Index Increment Measurement for Ml 18). During the procedure development for the M118 program, it was demonstrated that the dn/dc value varies depending on the purity of the material used. One parameter, water content, was a primary consideration and any residual moisture needed to be carefully taken into account in the concentration calculations. This point had not been evaluated during the first measurement of the dn/dc of Glatiramer acetate, and it can be of particular concern, as water content levels of up to 15% w/w are possible in Glatiramer acetate.

A New dn/dc value was then re-measured and a value of 0.184 mL/g was obtained, which included correction for sample moisture.

7.2 Impact of the dn/dc change on the data

A change in dn/dc value from 0.153 mL/g to 0.184 mL/g significantly shifted the molar mass results obtained on Glatiramer acetate RLD. This is shown in Table 2, where the results obtained with a 0.185 mL/g value (0.185 mL/g is a generic dn/dc value usually used for proteins, see Attachement 2) are

compared to results obtained with the original 0.153 mL/g value.

Table 2: Molar Masses measured on various lots of RLD as a function of the dn/dc

RLD Lot #	**dn/dc=0.153 mL/g**			
	Mn	**Mw**	**Mp**	**PD**
lot 538215	9790	12430	10030	1.270
lot 538215	9755	12330	10050	1.264
lot 538215	9552	12620	9921	1.321
lot 538072	8576	11840	9409	1.380
lot 538121	8383	12170	9959	1.452
lot 538217	9722	12850	10230	1.322
lot 538223	9333	12640	9981	1.355
lot 538225	9190	12760	10240	1.389
lot 538237	8817	12420	9985	1.409
lot 538238	8722	12250	9728	1.404
lot 538251	8370	11920	9767	1.424
lot 538261	8535	11880	9508	1.392
lot 538269	7893	11170	9063	1.416
lot 538276	7753	11530	9627	1.487
Average of RLD (12 Lots)	**8757**	**12155**	**9794**	**1.392**

[cont.]

RLD Lot #	dn/dc=0.185 mL/g			
	Mn	Mw	Mp	PD
lot 538215	8096	10280	8295	1.270
lot 538215	8068	10200	8314	1.264
lot 538215	7900	10430	8205	1.321
lot 538072	7092	9795	7782	1.381
lot 538121	6933	10070	8236	1.452
lot 538217	8040	10630	8458	1.322
lot 538223	7781	10460	8254	1.355
lot 538225	7600	10560	8466	1.389
lot 538237	7292	10280	8258	1.409
lot 538238	7213	10130	8045	1.404
lot 538251	6922	9858	8078	1.424
lot 538261	7058	9825	7863	1.392
lot 538269	6527	9240	7495	1.416
lot 538276	6412	9537	7962	1.487
Average of RLD (12 Lots)	**7247**	**10055**	**8099**	**1.392**

8.0 Evaluation of the SEC-MALS methodology

Beyond the exact value of dn/dc appropriate to use in the molar mass calculation, several questions remain. The molar masses obtained with the new value were still not consistent with the RLD label. Per the label, the RLD should have a molar masses around 7,000 Da. The best value that would be consistent with the middle of the label range is the number average molar mass (Mn). The weight average molar masses (Mw) were consistently out of the label range 5,000 9,000 Da and the molar masses at the apex (Mp) were near 8,100 Da.

Limitation of the light scattering approach were assigned as the cause of the inconsistency with the label. The Rayleigh law calls for the use of an average refractive index increment, which may not be appropriate for accurate characterization of a low molar mass distribution (MM <10,000 Da).

As the consistency with the label was critical for further development of Glatiramer acetate, it was decided to consider the method described by the innovator which calls for the use of synthetic peptides with given amino acid sequences as calibration standard. The development of the size exclusion method is detailed in Development Report (M356-DEV-004 Molar Mass Determination of Glatiramer acetate and Glatiramer Acetate Injection Using Size Exclusion Chromatography with Refractive Index Detection or UV Detection). The method developed only permits the determination of the molar mass at the top of the Apex (Mp), as the calibration standard set described by the innovator does not cover the entire range of the molar mass distribution of Glatiramer acetate. Mp results around 7,000 Da are obtained for RLD, as seen in Table 3, which is consistent with the label claim.

Table 3: Results obtained with Peptide Standard method

RLD Lot#	Mp (Da)
538215	7190
538261	7168
538473	7140

9.0 Future Work

Although the molar mass method using the innovator peptide calibration standard may not be long term solution, it has the advantage of being consistent with the RLD label. It will serve as reference for different approaches that will be developed in the future.

10.0 Conclusion

The Glatiramer acetate label (5,000 Da to 9,000 Da) is highly dependent on the method used to generate the molar mass results. The characterization of the molar mass distribution of Glatiramer acetate by SEC-MALS is not currently appropriate to support further development of that material. A method using peptide standards has been implemented. This method only allows the determination of the molar mass at the top of the Apex (Mp), as the calibration standard set described by the innovator does not cover the entire range of the molar mass distribution of Glatiramer acetate. Higher molar mass peptide standards are currently being prepared to allow the method to characterize the entire molar mass distribution. Once established, the upgraded method using peptide standard will serve as reference method for future method development.

11.0 Data References

Study	Notebook	Pages	Dates
Dn/dc measurement	86	57-59	02-Jun-05
Dn/dc measurement	189	99-100	27-Oct-06
	189	103-107	30-Oct-06
	189	108-109	06-Nov-06
MM measurements	260	178	19-Apr-07
	326	45-46	15-Jun-07

12.0 Attachments

12.1 Attachment 1: Measurement of dn/dc in Reference Listed Drug - June 05

1.0 Introduction

When using Size Exclusion Chromatography coupled with Multi-Angle Light Scattering (SEC-MALS) to determine the molar mass of a compound, one of the critical parameters is the change in refractive index with concentration (dn/dc). This value describes how much the refractive index of compound solution changes with respect to the concentration of the solute. The dn/dc value is specific to its respective compound, so it is necessary to calculate it correctly. The purpose of this experiment was to determine the dn/dc for Glatiramer acetate for use in further measurements of molar mass.

2.0 Experimentals/Materials/Method

Reference Listed Drug (RLD) was dialyzed prior to the experiment in order to remove the mannitol used

as an excipient. 100 mL of a 2.01 mg/mL stock dilution of dialyzed RLD (Lot #538121) was prepared on 05/18/05. The mobile phase was 0.2 M Sodium Sulphate with 0.05% Sodium Azide pH 6.5. Five dilutions were made and are presented in Table I below. Those solutions were injected, starting with the least concentrated. A blank injection of mobile phase was performed prior to and after the injection of the samples. The solutions were injected directly into the Optilab rex using a syringe pump. This is necessary to ensure 100% mass recovery. Data collection was monitored using the Astra V program.

Table I: Dilutions of a 2.01 mg/mL Extracted RLD solution

Dilution	m (Stock Solution)	m (total)	Concentration of solution (mg/ml)
10%	1.03g	10.00g	0.207
25%	2.50g	10.00g	0.503
40%	4.02g	10.01fl	0.809
60%	6.01g	10.01g	1.209
80%	8.01g	10.01g	1.612
100%	10.00g	10.00g	2.014

3.0 Results

The samples were injected until a stable plateau was observed as seen on Figure 1.

chromatograms

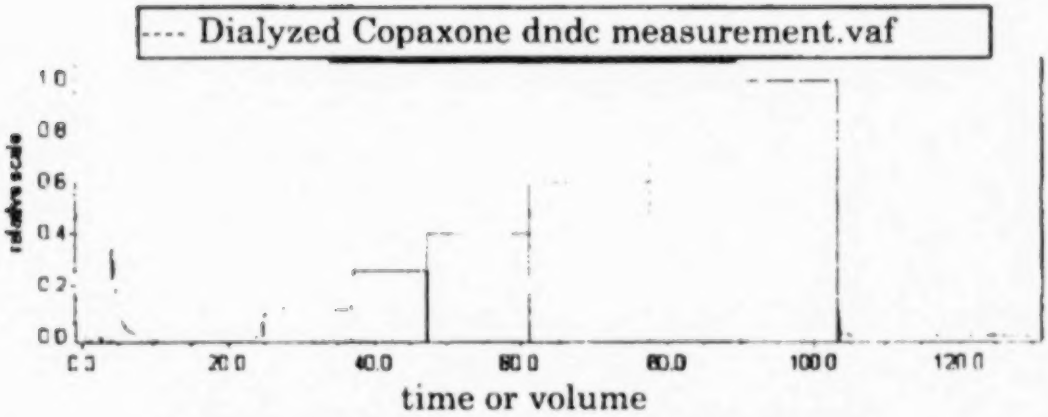

Figure 1: Chromatogram of collected signal

Once all of the injections were made, a baseline was drawn and a portion of each plateau was isolated.

Define peaks

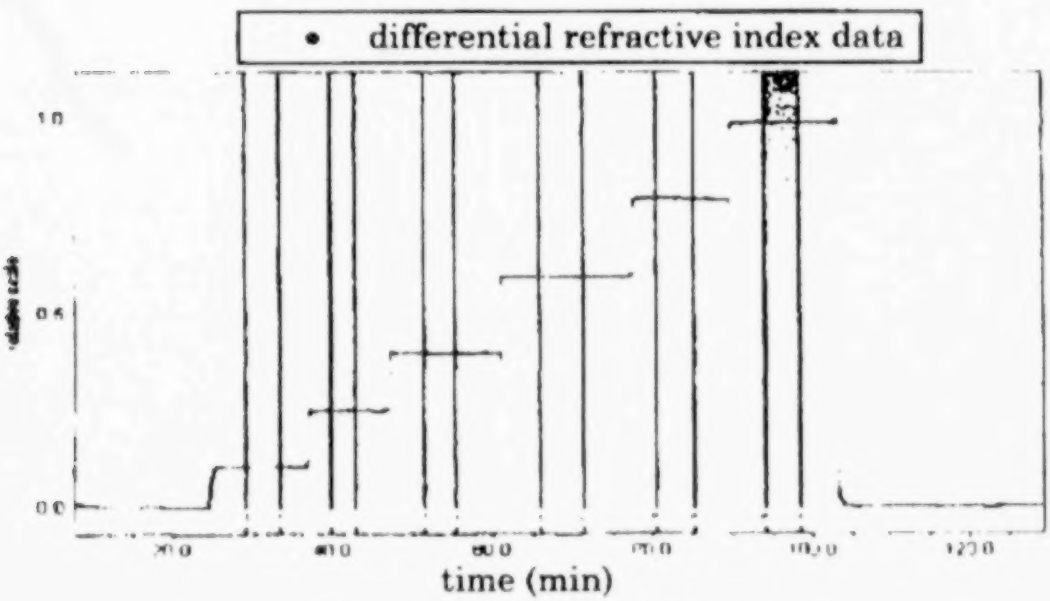

Figure 2: Isolation of data

The exact concentrations of the solutions injected were associated to each peak and the regression

curve was generated, as displayed on Figure 3. The relative scale used for the real time off-line measurement is converted into a differential refractive index scale during data computation.

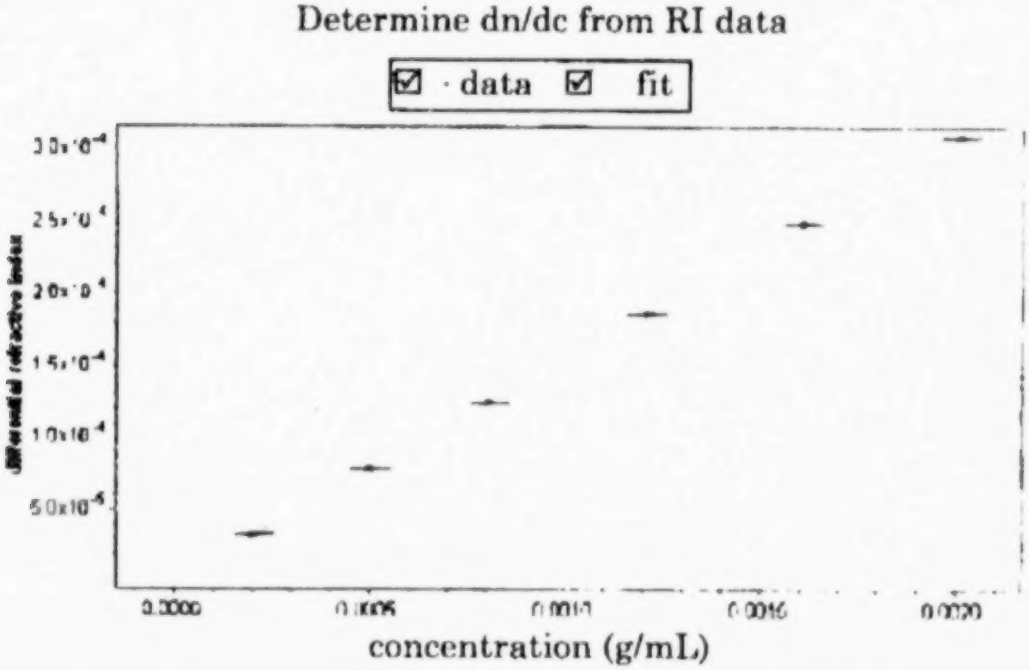

Figure 3: Refractive index vs. concentration

The value of the slope of the linear fit obtained for the differential refractive index vs. concentration is equal to the dn/dc of the compound. A **dn/dc=0.1531 mL/g** using a 1st degree fit was determined, with a R^2=1.00.

Using this value, and the chromatographic conditions presented in Table II, molecular weight data were calculated for different RLD samples previously analyzed and are presented in Table III.

Table II: Chromatographic conditions

HPLC	Agilent HP 1100 system
Mobile phase	0.2M Sodium Sulphate pH 6.5, with 0.05% Sodium Azide
Columns	Tosoh TSKgel G3000SW$_{xl}$ (7.8 mm x 30cm), Tosoh TSKgel G2000SW$_{xl}$ (7.8 mm x 30cm), Tosoh Guard column (6mm x 4cm)
Column temperature	Ambient
Injection volume	100 µL of a 10 mg/mL solution
Detectors	Wyatt miniDawn MALS detector
	Wyatt Optilab rEX RID detector
RID temperature	25°C
Run time	60min
Injections per sample	5
Alignment/ Normalization	1 BSA 1 mg/mL

Table III: Molar mass measurements on RLD samples

Samples	Lot#	Mw (Da)	Mn (Da)	PD
Extracted RLD	538121	11850	5800	2.04
RLD	538072	11450	5700	2.01

The molar mass results on extracted RLD was consistent with the ones observed on RLD, based on expected lot to lot variability. A chromatogram of RLD Lot# 538072 is shown in Figure 4.

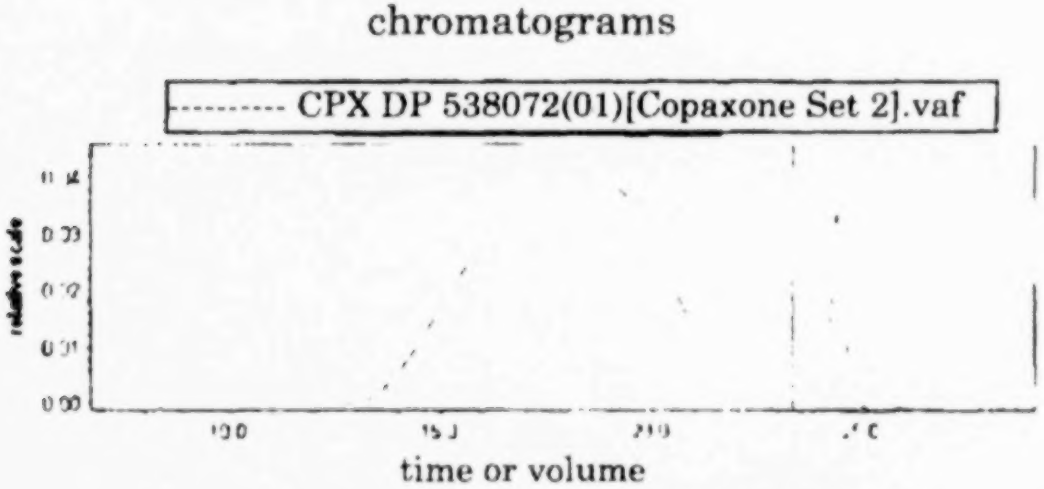

Figure 4: Chromatogram of RLD Lot#538072

4.0 Conclusion

A dn/dc value of 0.153 mL/g was determined for Glatiramer acetate. The dn/dc value is the result of one determination. The stock solution was kept 15 days at 4°C before the dilutions and measurements were performed. Additional determination of dn/dc are required to confirm this initial measurement. Moreover, the chromatographic conditions used to analyze the RLD samples have not been validated. If during a method optimization step, the mobile phase needs to be modified, the dn/dc value will have to be re-measured.

5.0 Data References

Study	Notebook	Pages	Dates
Dn/dc measurement	86	57-59	02-Jun-05

12.2 Attachment 2: Refractive Index Increment Measurement, literature review

The knowledge of the refractive index increment (dn/dc) of a macromolecular distribution is critical for the accurate molar mass determinations by light scattering. A summary of the literature review done to support the methodology developed in Analytical Development group to measure the dn/dc is presented. The literature review intends to capture "State of the Art" practice to perform SEC-LS measurements, and to answer the following questions:

What dn/dc values do the authors who do not measure it themselves use?

When they are measuring the dn/dc value, how do they do?

What are the parameters influencing the dn/dc?

1.0 Typical dn/dc values used for peptides/proteins

Although the exact dn/dc value ensures better accuracy of the molar mass, some authors prefer assuming a value.

Oliva *et al* [28] used **0.186 mL/g** for recombinant human growth hormone and ß-lactoglobulin. More generally, they also report that for proteins that contain only polypeptides (no carbohydrate), the dn/dc is constant (**~0.190 mL/g**).[29]

Camerini-Otero *et al* mentions a generic value for dn/dc as well. They state that in 0.1 0.2 M ionic strength solvent, **0.190 mL/g** can be adopted as a mean value for the dn/dc (measured at 436 nm) of "most" proteins.[30]

Folta-Stogniew *et al*[31] used a dn/dc value of **0.185 mL/g** for proteins (15 proteins analyzed, Mw ranges from 12 to 470kDa, Wyatt instrumentation) when analyzed in a 20 mM HEPES buffer, 100 mM KCl , and a dn/dc value of **0.186 mL/g** for the analysis performed in a 20 mM phosphate buffer,

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[28] "Comparative study of protein molecular weights by size-exclusion chromatography and laser-light scattering", Oliva A., Llabres M., Farina J.B., *Journal of Pharmaceutical and Biomedical Analysis*, 25, 833-841 (2001)

[29] "Applications of Multi-Angle Laser Light-Scattering Detection in the Analysis of Peptides and Proteins", Oliva A., Llabres M., Farina J.B., *Current Drug Discovery Technologies*, 1, 229-242 (2004)

[30] "Molecular Weights, Dispersion of Refractive Index Increments, and Dimensions from Transmittance Spectrophotometry, Bacteriophages R17, T7, and PM2, and Tobacco Mosaic Virus", Camerini-Otero R, Franklin R, Day L, *Biochemistry*, **13**(18), 3763 (1974).

[31] "Determination of Molecular Masses of Proteins in Solution: Implementation of an HPLC Size Exclusion Chromatography and laser Light Scattering Service in a Core Laboratory" *Journal of Biomolecular Techniques*, **10**(2), 51-63 (1999)

150 mM NaCl. They refer to the work of Wen *et al*[32] to support the choice of their refractive index increment values.

Wyatt recommends the use of a dn/dc value of **0.185 mL/g** for peptides and proteins, when using their instrumentation (690 nm).

2.0 Dn/dc measurement procedure

When performed, the measurement of the dn/dc of a macromolecule in a specific solvent is conventionally made off-line.

The preparation of the sample itself is sometimes emphasized in the literature reviewed. Kratohvil *et al*[33] details that the concentration of the solutions used in the dn/dc measurement is determined from the weight of a material (bovine plasma albumin) dried at 105°C under vacuum. Stating *et al*, who worked on a procedure to measure the dn/dc on-line, present dn/dc results obtained on dialyzed proteins as more accurate.[34] They however acknowledge that

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[32] "Size-Exclusion Chromatography with On-Line Light-Scattering, Absorbance, and Refractive Index Detectors for Studying Proteins and Their Interactions", Wen J., Arakawa T., Philo J.S., *Analytical Biochemistry*, **240**, 155-166(1996)

[33] "On the Refractive Index Increment of Bovine Plasma Albumin at Low Concentrations", Kratohvil J. P., Dezelic G., Dezelic N., *Archives of Biochemistry and Biophysics*, **106**, 381-385 (1964)

[34] "Complete On-Line Determination of Biopolymer Molecular Weight via High-Performance Liquid Chromatography Coupled to Low-Angle Laser Light Scattering, Ultraviolet, and Differential Refractive Index Detection", Stuting H., Kruli I., *Anaytical Chemistry*, **62**, 2107-2114 (1990)

an extensive 3-4 days dialysis is impractical in today's world, and the dn/dc results on dialyzed materials (R Nase A, Protropin, Crescormon, ß-lact A, BSA) do not significantly differ from the ones obtained on "technically pure" proteins. Norberg and Sundelof[35] describe the stringent precautions they took to prepare solutions prior to differential refractometer calibration and refractive index increment measurements. The calibration standards they used were dried until constant weight.

3.0 Important parameters for the refractive index increment

The main parameters influencing the refractive index increment[36] are:

The molar mass of the polymer. The dn/dc increases with the chain length, until it reaches a constant value above a certain molar mass which is about 10,000 Da. It is highly recommended to use an actually measured refractive index increment for the light scattering studies of low molar mass polymers. When the molar mass of a large distribution is to be characterized, it is conventional to determine the refractive index increment of the mixture, and to apply this value over the whole distribution. When dealing with a large distribution of low molar mass species,

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[35] Norberg P.N., Sundelof L.-O., Makromol. Chem. **77**, 77-89 (1964)

[36] "Light Scattering from Polymer Solutions", Chapter 6, M.B. Huglin, Academic Press, London and New York (1972)

uncertainties are obviously introduced doing so.

The composition of the polymer. The refractive index increment of a copolymer is known to be a linear function of its composition. To our knowledge, no literature has however been reviewed to support that relationship with peptides/proteins.

The solvent. The solvent is one of the main factors influencing the refractive index increment. As shown on Table a for casein,[11] the solvent can vary widely, especially when single solvent is compared to mixed solvents.

Table a: Dn/dc values obtained for Casein in various solvents

Solvent	**Dn/dc (mL/g)**	**T(°C)**
0.25 N KOH	0.149	25
0.25 N KOH / 25% Ethanol	0.158	25
0.25 N KOH / 50% Ethanol	0.149	25
0.25 N KOH / 75% Ethanol	0.125	25
Water	0.181	

The dn/dc is a linear function of the refractive index of the solvent. This has been shown with a reasonable degree of accuracy for single and mixed solvents. The problem with mixed solvents is however that one solvent can selectively adsorb more on the polymer than the other and this can affect the light scattering data. The study of the light scattering data in Polymer-mixed solvent

system is described by Huglin and Strazielle, and the authors describe well the level of complexity introduced by the use of a mixed solvent.[37]

External factors. The wavelength and the temperature have more minor effects. The specific refractive index increment increases with the decrease of the wavelength it is measured at (function of $1/\lambda^2$ and $1/\lambda^4$). The temperature effect depends on the polymer-solvent system, and can be either positive or negative, more rarely zero.

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[37] "Light Scattering from Polymer Solutions", M. B. Huglin, Chapter 6 p 187-195, Chapter 15 p 633-669 Academic Press, London and New-York (1972)

[Excerpt from PTX 219-R: Excerpt from Sandoz's ANDA]

* * *

Glatiramer Acetate Injection, 20 mg/mL
3.2.S.3.1 Elucidation of Structure and other Characteristics

Sandoz Inc.
26 December 2007

Redacted

3.2.S.3.1.3.2 Mass Profile

3.2.S.3.1.3.2.1 Introduction

Table 18 is a summary of the different analytical techniques that were used to evaluate the mass profile of Glatiramer Acetate. The first method is a quality release method (see Section 3.2.S.4). Due to the relatively narrow range of peptide calibration standards, this method is optimized to measure Mp, the molar mass at the peak apex. The second method is used to evaluate the full molar mass distribution of Glatiramer Acetate with protein standards that are used to calibrate the retention time axis over the polypeptide distribution. The use of protein standards gives relative results and is used as a comparison tool to characterize the molar mass distribution. A description of each method and the corresponding results from the analysis of the samples described in Section 3.2.S.3.1.1.3 is presented in the following sections.

Table 18. Analytical Methods used to Evaluate Mass Profile

Analytical Method	Section
Molar Mass (Mp) [SEC-RI]	3.2.S.3.1.3.2.2
Molar Mass Distribution [SEC-UV]	3.2.S.3.1.3.2.3

3.2.S.3.1.3.2.2 Molar Mass (Mp) by SEC/RI using Peptide Standards

INTRODUCTION

The Copaxone® package insert lists the average molecular weight of Glatiramer Acetate as 5,000 to 9,000 Da. The average molecular weight is an important structural property which is determined by Size Exclusion Chromatography (SEC) using peptide standards. The average molar mass is measured and reported as Mp (molar mass at the apex of the peak).

ANALYTICAL METHOD

The analytical method developed for the determination of the molar mass at the apex of the peak (Mp) is based on Size Exclusion Chromatography with two columns connected in series using TSKgel G3000 SW_{XL} and G2000 SW_{XL} and with detection based on Refractive Index detection. Nine peptide reference standards with amino acid compositions consistent with Glatiramer Acetate covering the molecular weight range from 1,500 Da to 12,000 Da are used to calibrate the retention time axis in order to determine an accurate measurement of Mp.

The nine peptide reference standards were qualified for their intended use (identity, quality, potency, and purity). Certificates of analysis, spectroscopic, and physicochemical data for the peptide reference standards are provided in Section 3.2.S.5.

RESULTS FROM ANALYSIS

The test samples (see Section 3.2.S.3.1.1.3) were determined for molar mass (Mp). Table 19 contains a summary for the drug substance lots and Table 20 contains a summary for the drug product lots. The results from the Reference Listed Drug lots are also reported in Table 20. Representative molar mass size exclusion chromatograms for Glatiramer Acetate Injection Lot CT0743 and Reference Listed Drug Lot 538455 are shown in Figure 12 and Figure 13.

Table 19. Molar Mass (Mp) for Glatiramer Acetate

Sample	Lot	Results-Mp (Da)
Glatiramer Acetate[1]	077K7277	Mean of 8407 (n= 2)
Glatiramer Acetate	087K7253	Mean of 7275 (n= 2)

[1] Exhibit Batch

Table 20. Molar Mass (Mp) for Glatiramer Acetate Injection and Reference Listed Drug

Sample	Lot	Results-Mp (Da)
Glatiramer Acetate Injection[1]	CT0743	Mean of 8274 (n = 2)
Glatiramer Acetate Injection	C10750	Mean of 7426 (n = 2)
Reference Listed Drug	See Section3.2.S.3.1.1.3	5943.7491
Equivalence Criteria[2]	See Section3.2.S.3.1.5.1	5000-9000

[1] Exhibit Batch

[2] Limit from Reference Listed Drug package insert

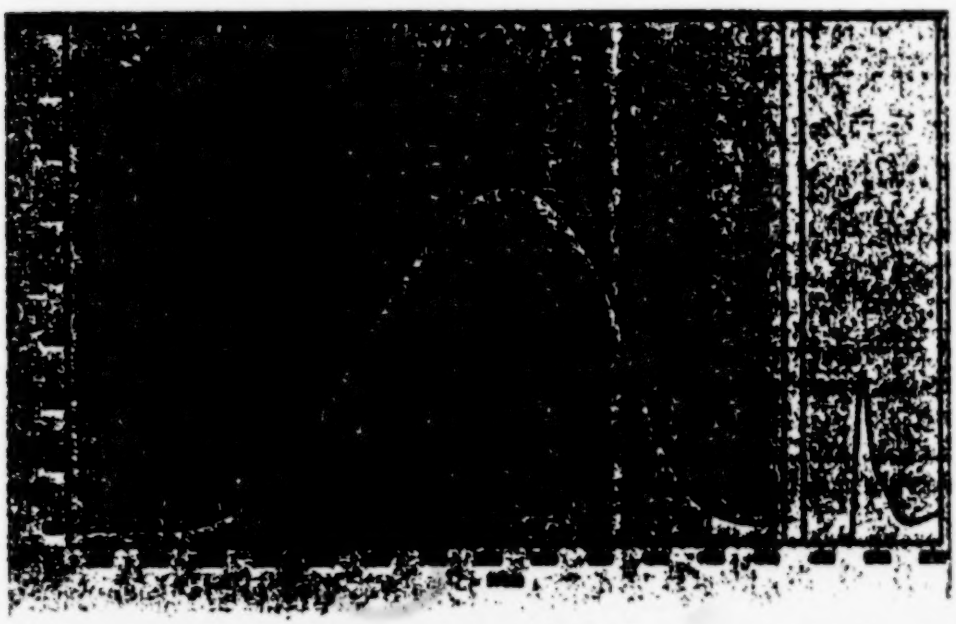


Figure 12. Molar Mass SEC Chromatogram of Glatiramer Acetate Injection by SEC/RI using Peptide Standards, Lot CT0743

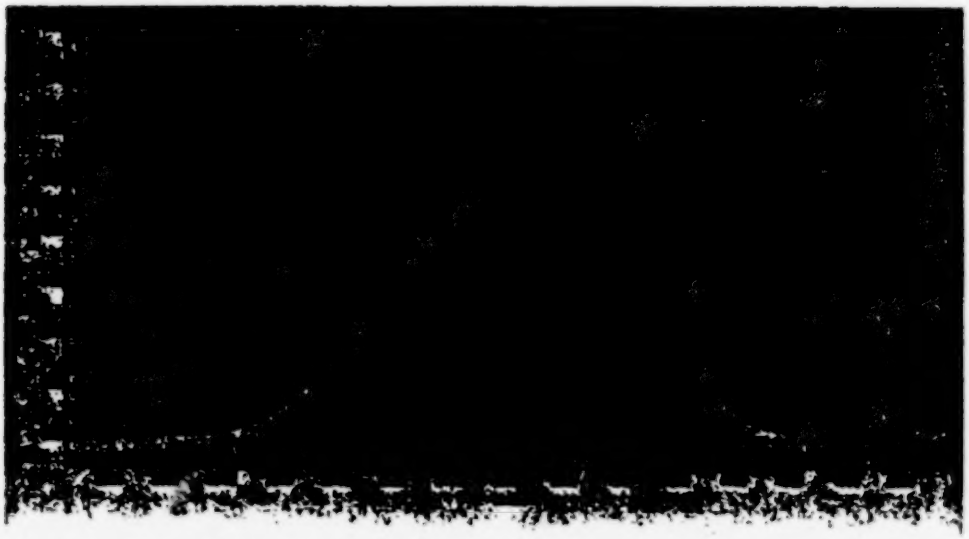


Figure 13. Molar Mass Chromatogram of Reference Listed Drug by SEC/RI using Peptide Standards, Lot 538466

INTERPRETATION OF RESULTS

Results from method qualification studies on the precision of the method are summarized in Table 21, which show a % RSD of 1.0% for the determination of Mp in repeatability experiments and an %RSD of 1.8% when the analysis is performed by multiple operators, over multiple days with two different columns. The results demonstrate the repeatability of the molar mass assay.

Table 21. Results from Precision Studies

Study	Design	Results
Repeatability	Replicate injections of a Glatiramer Acetate Test Sample	%RSD 1.0, n=5
Intermediate Precision	Replicate Determinations of Glatiramer Acetate in a Test Sample by a second analyst, using a different column, on a different day	%RSD 1.8, n=10

The equivalence criteria are based on the RLD label, 5,000 9,000 Da. The results in Table 20 show an Mp range of 5,943 to 7,495 Da; a significantly narrower range for the Reference Listed Drug lots examined than the labeled claim. While it is clear that the results for molar mass are method dependent, the results obtained with the peptide standards indicate that the method described above is consistent with the Innovator's label claim. The fact that there is a difference between the experimental minimum and maximum range reported for the retrospective analysis of the RLD and the label claim illustrates the limitations of the sampling protocol. This observation also demonstrates the rationale for why a simple minimum and maximum equivalence range is not necessarily representative of the Innovator's material, where limits can be verified directly from the label claim.

The data for the Glatiramer Acetate exhibit batch (Lot 077K7277) and process batch, (Lot 087K7253), are within the label claim of 5000 to 9000 Da. The data for Glatiramer Acetate Injection exhibit batch (Lot CT0743) and a second drug product batch (Lot CT0750) are also within this range.

The results of the analysis of molar mass (Mp) using peptide standards demonstrate that Glatiramer Acetate and Glatiramer Acetate Injection are within the equivalence range (label claim) of the RLD.

3.2.S.3.1.3.2.3 Molar Mass Distribution by SEC/UV using Protein Standards

INTRODUCTION

The molar mass distribution of Glatiramer Acetate and Glatiramer Acetate Injection is also an important structural property of the drug substance and drug product which is determined by Size Exclusion Chromatography using protein standards. For purposes of characterizing the molar mass distribution of the polypeptide mixture, the ratio (Ip) of the Mw (weight average molar mass) to Mn (number average molar mass) of the samples and RLD are calculated.

ANALYTICAL METHOD

The analytical method developed for the determination of the molar mass distribution is based on Size Exclusion Chromatography (SEC) using a GE Healthcare Superose 12 column with ultraviolet detection (UV). The chromatograms are calibrated using commercially available protein standards. Standard curves are prepared from a defined mixture of high and low MW protein standards which include: Insulin chain B (MW 3,496 Da), Aprotinin (MW 6500 Da), Ribonuclease A (MW 13,700 Da), Carbonic Anhydrase (MW 29,000 Da), Aldolase (MW 158,000 Da), and Ferritin (Mw 440,000 Da).

For purposes of characterizing the RLD polypeptide mixture and demonstrating equivalence between the test and RLD, molar mass distribution is characterized by Ip, which is the ratio of the Mw

(weight average molar mass)/Mn (number average molar mass).

RESULTS FROM ANALYSIS

The test samples (see Section 3.2.S.3.1.1.3) were determined for molar mass distribution (Ip). Table 22 contains a summary for Glatiramer Acetate Lots 077K7277 and 087K7253 and Table 23 contains a summary for Glatiramer Acetate Injection Lots CT0743 and CT0750. The results from the Reference Listed Drug lots are also reported in Table 23. Representative molar mass distribution chromatograms for Glatiramer Acetate Injection Lot CT0743 and Reference Listed Drug Lot 538455 are shown in Figure 14 and Figure 15, respectively.

Table 22. Molar Mass Distribution for Glatiramer Acetate

Sample	Lot	Mn	Mw	IP
Glatiramer Acetate	077K72771	23294	65378	2.8
Glatiramer Acetate	087K7253	16473	56810	3.5

1 Exhibit Batch

Table 23. Molar Mass Distribution for Glatiramer Acetate Injection and Reference Listed Drug

Sample	Lot	Mn	Mw	IP
Glatiramer Acetate Injection[1]	CT0743	23076	65047	2.8
Glatiramer Acetate Injection	CT0750	16228	56061	3.5
Reference Listed Drug	See Section 3.2.3.3.1.1.3	14981-19564	43712-54788	2.6-3.2
Equivalence Criteria[2]	See Section 3.2.S.3.1.6			2.0-4.0

[1] Exhibit Batch

[2] Equivalence Criteria based on 75% of the RLD minimum and 125% of the RLD maximum

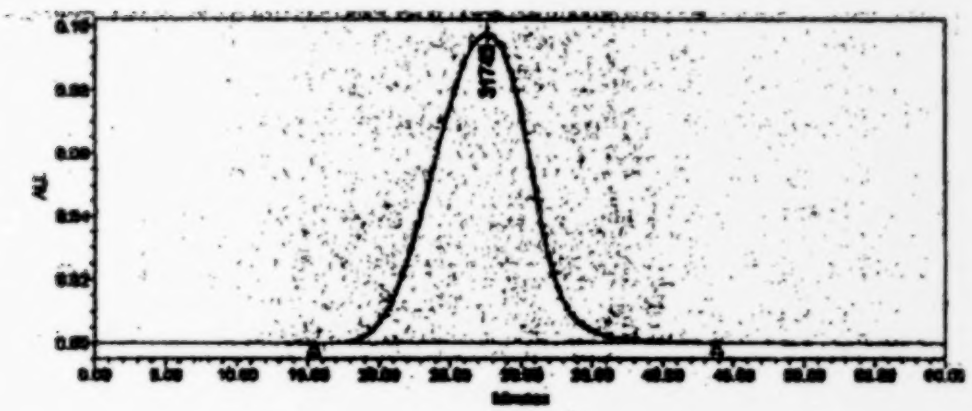


Figure 14. Molar Mass Chromatogram of Glatiramer Acetate Injection by SEC/UV using Protein Standards, Lot CT0743

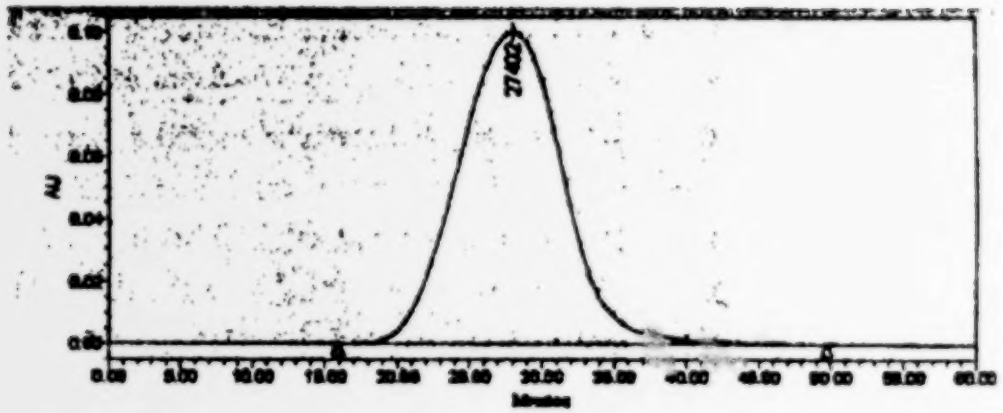


Figure 15. Molar Mass Chromatogram for the Reference Listed Drug by SEC/UV using Protein Standards, Lot 538455

INTERPRETATION OF RESULTS

Results from method qualification studies on the precision of this assay are summarized in Table 24, which show the % RSD of 2.2% for multiple determinations on the same day and an overall %RSD of 2.8% when performed over multiple days. The results demonstrate the repeatability of the molar mass distribution assay.

Table 24. Results from Precision Studies

Study	Design	Results (Ip)
Repeatability	Replicate injections of a Glatiramer Acetate	%RSD 2.2, n=5
Intermediate Precision	Replicate Determinations of Glatiramer Acetate over two days	%RSD 2.8, n=10

The equivalence criteria is based on applying a factor of 75% of the RLD minimum and 125% of the RLD maximum derived from the analysis of twenty batches of the RLD. The justification of the

equivalence criteria is presented in Section 3.2.S.3.1.6.

The data for the Glatiramer Acetate exhibit batch (Lot 077K7277) and process batch (Lot 087K7253), are within the equivalence criteria of 2.0 to 4.0 for the measurement of polydispersity (Ip). The data for Glatiramer Acetate Injection exhibit batch (Lot CT0743) and a second drug product batch (Lot CT0750) are also within this range.

The results of the analysis of molar mass distribution using protein standards demonstrate that Glatiramer Acetate and Glatiramer Acetate Injection are within the equivalence range based on the analysis of the RLD.

[Excerpt from PTX 318-R: Excerpt from Mylan's ANDA]

* * *

MYLAN

1.12.15 REQUEST FOR WAIVER OF IN VIVO STUDIES

GLATIRAMER ACETATE SOLUTION FOR SUBCUTANEOUS INJECTION, 20MG/ML

Mylan Pharmaceuticals, Inc. hereby requests a waiver of *in vivo* bioequivalence studies for Glatiramer Acetate Solution for Subcutaneous Injection, 20 mg/mL in accordance with 21 CFR 320.22 which states that bioequivalence may be considered self-evident in cases where the drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

Mylan's glatiramer acetate product meets these criteria based on the following:

1. Both Mylan's glatiramer acetate drug product and Copaxone®, are solutions intended solely for subcutaneous injection.

2. Both Mylan's glatiramer acetate drug product and Copaxone® each contain one inactive ingredient, mannitol, in water at a concentration of 40 mg/mL.

3. Both Mylan's glatiramer acetate drug product and Copaxone® contain the active pharmaceutical ingredient, glatiramer acetate, in water at a concentration of 20 mg/mL.

4. Mylan's active pharmaceutical ingredient has been demonstrated to be the same as Copaxone® through a rigorous characterization program encompassing a number of independent analytical and biological tests. The results of the tests summarized below are provided herein.

   a. The average molecular weight of the Sponsor's product, determined by multiple analytical techniques, was the same as Copaxone®. Peak average molecular weight of the Sponsor's product was within the 5000-9000 Da range specified in the approved labeling for Copaxone®.

REDACTED

1. Demonstration of sameness of the active pharmaceutical ingredients in the Sponsor's product and Copaxone®

A rigorous program was undertaken to characterize the glatiramer acetate in the Sponsor's product (referred to hereafter as GMA) and that in Copaxone®. This program comprised a number of independent analytical and biological techniques summarized below.

Analytical Characterization

- Molecular weight determination
    - Size-exclusion chromatography (SEC) with ultraviolet (UV) and refractive index (RI) detection using alanine-glutamic acid-tyrosine-lysine (AEYK) polypeptides as molecular weight standards
    - SEC with light scattering (LS) detection
    - SEC with MALDI-TOF-MS[38] detection

REDACTED

REDACTED

[38] MALDI-TOF-MS = matrix-assisted laser desorption time of flight mass spectrometry

Table 1: Lot numbers of GMA and Copaxone® used in the analytical characterization

GMA	Copaxone®
GMA/001/09	P53032
GMA/002/09	P53036
GMA/003/09	P53042

REDACTED

2. Analytical Characterization

2.1. Molecular Weight Determination

Multiple independent analytical techniques were used to characterize the molecular weights of GMA and Copaxone®. Importantly, orthogonal techniques were used. That is, the principles by which these techniques generated molecular weight information were completely independent of each other.

The assessment of the molecular weights of GMA and Copaxone® was performed using three orthogonal analytical techniques: (i) SEC-UV/RI with AEYK polypeptide calibration standards (ii) SEC-LS, and (iii) SEC-MALDI-TOF-MS. These techniques, their principles of operation, and the information obtained from each are summarized in Table 2.

Table 2: Orthogonal analytical techniques used in the characterization of molecular weights of GMA and Copaxone®

Technique	Operating Principle for MW Determination	Information Obtained
SEC-UV SEC-RI	Differential migration due to size-based partitioning of analytes into pores of stationary phase (SEC) External calibration with AEYK polypeptides of known molecular weight	Number average molecular weight (M_n) Weight average molecular weight (M_w) Molecular weight at SEC peak apex (M_p)
SEC-LS	Intensity of angularly scattered light Absolute technique; requires no calibration of columns	M_n, M_w, M_p
SEC-MALDI-TOF-MS	Ion transit time in mass spectrometer flight tube	Peak mass across discrete fractions of SEC peaks M_p

For the SEC-UV, RI, and LS analyses, 3 molecular weight parameters, defined below, were determined for each lot of product[39]. Two of the parameters, M_n

[39] M_n and M_w were not determined in the SEC-MALDI-TOF-MS analysis.

and M_w are based on statistical moment analyses of the molecular weight distributions. The third parameter, M_p, was obtained directly from the SEC chromatograms. These molecular weight parameters are defined briefly below.

Number average molecular weight (M_n)

M_n can be interpreted as a simple numerical average of the individual molecular weights in the product. It is calculated using equation 1 where N_i is the number of molecules having a particular mass M_i.

$$(1) \qquad M_n = \Sigma M_i N_i / \Sigma N_i$$

Weight average molecular weight (M_w)

M_w reflects the fact that the higher molecular weight components contribute a larger fraction to the overall molecular weight of the sample than do the smaller components. Thus Mw is said to be "weighted" according to molecular weight. M_w is calculated using equation 2. As in Equation 1, N_i is the number of molecules having a particular mass M_i

$$(2) \qquad M_w = \Sigma M_i^2 N_i / \Sigma M_i N_i$$

Because it reflects a greater contribution of higher molecular weight components, Mw will be larger than M_n in any polydisperse sample (a sample with a range of different molecular weight components).

Peak molecular weight (M_p)

M_p is the molecular weight at the apex of the SEC peak.

2.1.1. SEC-UV/SEC-RI

The operating principle of size-exclusion chromatography (SEC) is the differential migration of polymers based on their ability to partition into the pores of the stationary phase particles. Small molecules readily enter the pore space and experience longer transit times through the column, while larger molecules are sterically excluded from the pore space and experience shorter transit times. As a result, retention times in SEC correlate inversely with molecular size. Molecular weights are determined using calibration curves constructed from the retention times of known molecular weight standards.

However, SEC retention behavior based strictly on molecular weight (size) may not be realized in practice. For example, polymers may interact chemically with the stationary phase, or different polymers may have the same molecular weights, but different shapes, which may differentially affect the ability to partition into the pore space. It is therefore imperative in SEC to have a good set of calibration standards in order to obtain accurate results. That is, the standards should be chemically as similar as possible to the polymer of interest.

For this reason, the calibration standards used for the SEC-UV and SEC RI analyses of GMA and Copaxone® were polypeptides consisting of the same

4 amino acids present in Copaxone®: alanine, glutamic acid, tyrosine, and lysine. These polypeptide standards were synthesized by GL Biochem (Shanghai, China). The molecular weights and amino acid sequences of the polypeptide standards are shown in Table 3.

TABLE 3: MOLECULAR WEIGHT CALIBRATION STANDARDS USED IN THE SEC-UV AND SEC-RI EXPERIMENTS

Standard	Amino Acid Sequence	MW (Da)
MWS-35	AKKYAKKEKAAKKAYKKEAKAKAAEA AAKEAAYEA	3757
MWS-45	AKKYAKKAKAEKAKKAYKAAEAKKAA KYEKAAAEKAAAKEAAYEA	4790
MWS-56	AKYAKKEKAYAKXAEKAAKKAEAKAYK AAEAKKKAEAKYKAEAAKAAAKEAAYE A	6008
MWS-66	AKXKYAKKEKAYAKAKKAEAKAAKKA KAEAKKYAKAAKAEKKEYAAAEAKYKA EAAKAAAKEAAYEA	7040
MWS-77	AKKYAKKEAKYAKKAEKAAKKAEAKAY XAAEAKKKAKAEAKKYAKAAKAEKKEY AAAEAKYKAEAAKAAAKEAAYEA	8259
MWS-86	AKKYAKKEKAYAKKAEKAAKKAEAKAY KAAEAKKKAKAEAKKYAKAAKAEKKE YAAAEAKYKAEAAKKAYKAEAAKAAAK EAAYEA	9220

Amino Acid Single Letter Codes

A = Alanine; E = Glutamic Acid; Y = Tyrosine; K = Lysine

The SEC separations were carried out on dual Superose 12 agarose-based columns (10 x 300 mm) run in series with a mobile phase consisting of 0.1M ammonium acetate pH = 5.0. The flow rate was 1.0 mL/min. Detection was performed by UV at 280 ran and refractive index (RI). The results of these analyses are summarized in Table 4.

TABLE 4: MW RESULTS OBTAINED FROM SEC-UV AND SEC-RI USING THE AEYK POLYPEPTIDE MOLECULAR WEIGHT STANDARDS

Lot	*SEC-UV*			*SEC-RI*		
	M_n	M_w	M_p	M_n	M_w	M_p
GMA/001/09	5542	8757	6297	6010	9065	6339
GMA/002/09	5376	8558	6161	5937	9072	6274
GMA/003/09	5309	8468	6096	5863	9082	6325
Average	5409	8594	6185	5937	9073	6313
Std. Dev.	120	148	103	74	9	34
COP P53032	4865	8679	5635	5480	9336	5829
COP P53036	5031	8848	5798	5746	9417	6247
COP P53042	5212	9186	5942	5997	10012	6232
Average	5036	8904	5792	5741	9588	6103
Std. Dev.	174	258	154	259	369	237
Comparison of Averages	*SEC-UV*			*SEC-RI*		
	M_n	M_w	M_p	M_n	M_w	M_p
GMA	5409	8594	6185	5937	9073	6313
Copaxone®	5036	8904	5792	5741	9588	6103
Relative Difference	7.4%	-3.5%	6.8%	3.4%	-5.4%	3.4%

It is of interest that comparable results were found between GMA and Copaxone® in both the UV and RI

data sets. Under these conditions it is the tyrosine residues that are primarily being detected by UV at 280 nm, whereas RI is expected to respond more universally to the polypeptides, irrespective of primary structure. Thus, these results also imply comparable distributions of tyrosine-containing moieties in the products.

2.1.2. SEC-LS

Light scattering (LS) is a powerful tool for the determination of molecular weights of macromolecules. With an LS detector, scattered light intensity is proportional to the product of a molecule's concentration and its molecular weight (C^*MW). The use of a concentration detector (e.g. RI) in-line with an LS detector therefore permits the direct determination of molecular weight within each eluting fraction of an SEC peak. A key aspect of LS for the determination of molecular weight is that it is an absolute technique; no calibration standards are required for calibration of the columns. Thus one of the limitations of standard SEC, the need for calibration standards that mimic the analyte with respect to molecular composition, shape and adsorptive properties, is overcome.

The SEC-LS separations were carried out on dual Superose 12 columns (10 x 300 mm) run in series with a mobile phase consisting of 0.1M ammonium acetate pH = 5.0. The flow rate was 1.0 mL/min. Detection was performed with RI for concentration in series with light scattering at 90°. Results are provided in Table 5.

[Excerpt from PTX 969: Deposition Designation Clip Report of Frantisek Svec, Ph.D.]

Svec, Frantisek (Vol. 01) 10/28/2009 [Volume 1]

CONFIDENTIAL

1 CLIP (RUNNING 01:22:42.288)

Combination - C

SVEC1 COM 79 SEGMENTS (RUNNING 01:22:42.288)

1. **PAGE 5:14 TO 5:17 (RUNNING 00:00:10.633)**

[5]

MR. JAMES: Good morning, Dr. Svec.

Q Can you please state and spell your name for the record.

A Frantisek Svec. F-R-A-N-T-I-S-E-K, S-V-E-C.

2. **PAGE 6:05 TO 6:24 (RUNNING 00:00:48.000)**

[6]

Q You submitted a declaration in this case?

A Yes, I did.

Q Sitting here right now, are you aware of any changes that you would like to make to that declaration?

A Yes. Perhaps I would like to go back to the paragraph that is six --

Q Okay.

A -- which --

Q Perhaps we should -- we'll mark a copy. Let's -- I'll just interrupt you. I'm sorry. I'll just go ahead and mark a copy of your declaration with the exhibits.

This is the "Declaration of Frantisek Svec, Ph.D., in support of defendants Sandoz, Inc.'s --Inc.'s and Momenta Pharmaceutical, Inc.'s opening Claim Construction Brief." I guess we'll just mark these as Svec 1, et cetera.

(Document marked Svec Exhibit 1 for identification.)

3. PAGE 7:03 TO 9:23 (RUNNING 00:05:15.466)

[7]

THE WITNESS: Okay.

MR. JAMES: Q. Dr. Svec, if you could take a moment and flip through there and make sure that what I've handed you is an accurate copy of your declaration that you submitted in this case.

A Yes, it looks like the -- the accurate...

Q If you turn to paragraph 36, could you tell me the correction that you would like to make.

A Well, I am talking about the peak molecular weight here. I'm saying that this is not a true mathematical average, but it is commonly referred to as peak average.

While after signing this declaration, I went through the site finder, which is a database that is used by chemists, to see the literature and to find specific things in the literature, and I didn't find any hits when I tried to get the peak average molecular weight. So I am now of opinion that it's not that commonly referred to as a peak average, so I think I would now remove the word "commonly."

Q You would remove the word "commonly" from your expert declaration in paragraph 36?

A Yes.

[8]

Q But it is referred to as peak average. That is, peak molecular weight is referred to in your field as peak average?

A Sometimes, but certainly not commonly.

Q When you signed your declaration on October 6th, you believed that to be true; correct?

A Yes, I did.

Q And why is that, that you believed it to be true then?

A Well, because it looked like a -- an -- a wording that people might use. Because obviously, in the polymer chemistry, the averages are used quite often. I was -- I -- I didn't look at any specific literature, and that was my gutt feelings.

Q Is it your testimony that -- let me strike that.

Peak average -- let me strike that.

Peak molecular weight is a commonly used designation in your field for polymer distributions; correct?

A No. Peak molecular weight is a common expression used for a molecular weight period. You know, it's not for molecular weight distribution; it's for molecular weight.

[09]

Q What molecular weight does it indicate?

A It indicates molecular weight at the apex of the molecular weight distribution curve.

Q What information does the peak molecular weight value provide a person of skill in your field? What information does it provide them with respect to a particular polymer?

A Well, it provides value that shows what is the maximum at the -- the curve, the -- the molecular weight distribution curve. Nothing else.

Q Does that have any relationship to the number of molecules of the polymer that are coming out of the chromatogram at that time?

A Well, I -- I would put it this way, it says how many molecules or how -- what is the percentage or fraction or weight of molecules having that specific molecular weight.

Q So would it be fair to say that the peak molecular weight indicates the fraction of polymer molecules that are the most common in the sample you're testing?

A That's correct.

4. PAGE 17:05 TO 17:11 (RUNNING 00:00:32.330)

[17]

Q Does the patent indicate that any characterization is done of that copolymer that you mentioned?

A Well, I think there is mention to that in one of the examples. In example one, I guess, the patent tells that they used size exclusion chromatography for characterization.

5. PAGE 22:16 TO 22:20 (RUNNING 00:00:17.707)

[22]

Q Sure. We'll mark a copy of the patent.

I'm going to mark as Svec 2 a copy of United States Patent No. 5,800,808.

(Document marked Svec Exhibit 2 for identification.)

6. PAGE 23:02 TO 23:16 (RUNNING 00:00:30.443)

[23]

MR. JAMES: Well, let me try to lay some groundwork for this patent. This is patent 5,800,808.

Q I'll refer to it today as the '808 patent today, if that's okay; okay?

A (Witness nods head.)

Q You'll have to answer verbally so she can --

A Yes.

Q -- take down your answers.

A I thought I did.

Q Do you understand this to be one of the patents-in-suit in this case?

A Yes.

Q Have you re- -- reviewed the specification of this patent?

A Yes.

7. PAGE 25:15 TO 26:05 (RUNNING 00:01:21.614)

[25]

Q And what do you mean by "calculation of the molecular weight"?

A Well, you know, you have different types of molecular weight averages that describe specific polymer, and each of these specific average molecular weights that you can produce as a single number can be calculated from the -- from the results of -- of the gel filtration. This is not what is shown here.

Q To make sure I understand your answer, the calculations of average molecular weights is not shown in Example 1; is that your testimony?

[26]

A Well, there is -- in reality, there is not any evidence in this Example 1 that says how the molecular weights we spoke about previously have been obtained.

8. PAGE 26:06 TO 27:18 (RUNNING 00:02:22.935)

[26]

Q Okay. But the patent does describe the use of size exclusion chromatography?

A Yes.

Q Okay. Now, in 1994 or as of 1994, had you used size exclusion chromatography?

A You mean myself in the lab or –

Q In any sense of you. Whether you -- you at the lab bench, or you directing post docs or lab technicians or -- in any other sense of the word, had you used size exclusion chromatography as of 1994?

A Yes.

Q Okay. And on how many occasions had you used size exclusion chromatography?

A Well, size exclusion chromatography is a very common method for the determination of molecular weight of polymers, so it's essentially in each --well, I would say decently equipped lab that works with synthetic and nature -- in nature polymers.

Q Okay. Is it fair to say that you believe that in 1994 you were very familiar with size [27] exclusion chromatography?

A Well, I believe so.

Q And do you think that the person of ordinary skill in the art of the '808 patent, which we were looking at, would also, likewise, have been very knowledgeable about size exclusion chromatography?

A Well, it depends -- depends on what do you mean under the skilled in the art, okay.

Q I think in your declaration, which we marked as Svec Exhibit 1, in paragraph 12, you describe the person of ordinary skill in the art.

A Yes.

Q Do you think that person, as you have described them, would have been knowledgeable about size exclusion chromatography?

A That's right. Person like this will be knowledgeable.

9. PAGE 31:04 TO 35:18 (RUNNING 00:07:23.341)

[31]

Q In the size exclusion chromatography that you just described, when the polymer molecules -- you didn't describe them as being necessarily limited to polymer moleculars, but for the sake of asking my question, when the polymer molecules come out of the column and are detected by the detector, the detector then registers the UV absorption or the changes in optical density in some manner; correct?

A Yes, yes.

Q How is it registered?

A At the time of the mid-1990s or 1994, very likely we were using XY plotters to monitor this.

You could probably look at some kind of gauge, but not really any -- anything you can use to -- to demonstrate the molecular weight distribution.

Q What is an XY plotter?

A XY plotter is or was -- was a device or instrument where you have a piece of paper like this and you have a pen, which was on a moveable -- how do you call it -- device, you know, and it was, in fact, a volt meter, you know, that showed the voltage that [32] came up from the detector and registered the voltages continuously.

Q So the paper moved, and then the pen would move up to some point based on --

A Well, it's -- it's -- it depends. Sometimes moved the paper. Sometimes moved the pen.

Q Okay. But in any event, as each fraction came out of the column and was detected by the detector, the pen would move to the next coordinate on the X axis and then provide a -- some data point on the Y axis based on the detector's level of --

A Response.

Q -- response. Thank you.

And that created a curve --

A Yes.

Q -- correct?

A That's correct.

Q And that curve is called a chromatogram?

A It is called chromatogram.

Q So in 1994, size exclusion chromatography was known to generate a chromatogram --

A Yes.

Q -- is that right?

Once you had the chromatogram in 1994, how [33] did you create a molecular weight distribution curve?

A To do this, you need to calibrate your system. And then, using relatively simple mathematics, you may change the dilution times to molecular weight, or I would say recalculate, which is more accurate.

Q Can you describe how you would have calibrated the system?

A System is calibrated using a set of compounds with varying molecular weight that are well-characterized, preferentially very narrow molecular weight with very narrow molecular weight distribution, and you inject each of these calibrates in your system, and you see the response of the detector or, even better, you measure the retention time or the elution time, and you are getting a -- a plot of the retention times or, rather, molecular weight versus the retention times, so –

Q Molecular weight on the X axis --

A Yes.

Q -- and retention time on the Y?

A No, no, the other way around.

Q Okay. The other way around. Okay.

Molecular weight on the Y axis versus [34] retention time on the X axis.

A X axis.

Q And then based on that calibration for any given retention time in your chromatogram, you could read off what the molecular weight --

A Is --

Q -- was or –

A -- or was.

Q -- is, yes.

In that way you can then transfer the data from the chromatogram into a molecular weight distribution curve?

A No. You can just use -- you -- can you say that again?

Q I guess I'm just trying to make -- make sure I understand.

From the chromatogram that you generated from your size exclusion chromatography and this calibration curve that you've created now, you can then create the molecular weight distribution curve?

A That's right, yeah.

Q And on the chromatogram, the peak of the chromatogram corresponds to the peak molecular weight; correct?

A That's correct.

[35]

Q So the peak molecular weight doesn't require any calculation beyond calibrating your -- your column; correct?

A That's correct.

Q Okay. In 1994, this transfer of -- I'm not using the right word. Help me with a word here.

So when you have your chromatogram and you want to create your molecular weight distribution curve, what is that transformation called? How would you -- how would you describe that?

A I -- I don't think I have any specific word for this.

Q Okay.

A But certainly transformation is something that would be understood.

Q Okay. In -- in the patent, the figures show

10. PAGE 37:08 TO 37:13 (RUNNING 00:00:26.277)

[37]

The -- the percent of the mass of each fraction that comes out is not infinitely small on the chromatogram; correct?

In other words, there are slices that -¬they're not one millisecond wide. They're somewhat wider than that; correct?

11. PAGE 37:15 TO 38:02 (RUNNING 00:00:37.750)

[37]

THE WITNESS: Well, you know, you have to understand that this graph -- I mean, this curve, plot is not calculated from any fractions. This is not -- if that would be individual fractions, you cannot have a continuous curve.

MR. JAMES: Q. And why is that?

A Because you don't have all the points to fill out all the shape of the curve.

Q Okay. How many fractions would you need in order to create a curve like this?

A That would be the infinite number of [38] fractions.

12. PAGE 38:06 TO 40:18 (RUNNING 00:03:32.197)

[38]

Q Okay. In 1994, as of 1994, had you created any graphs like Figure 1 for any polymers that you were dealing with, percent of the total mass graphed against molecular weight?

A We typically create graphs that represent fraction of a specific mass against the molecular weight, but using percentages, nothing wrong.

And certainly, to answer your question, yes, we did.

Q And as of 1994, can you describe the process by which you would have graphed fraction of the mass versus molecular weight?

A I'm not sure I -- I -- I'm getting your –

Q Okay. I -- I thought that you said that you had graphed the fraction of the total mass that was made up of any one molecular weight fraction versus the molecular weight, that you had graphed that --

A Yes.

Q -- as of 1994?

A Yes.

[39]

Q Okay.

A Well, obviously, we had -- back to what I said a few seconds ago, if the goal for fractionation is to get the fractions, you cannot create this type of curve.

Q Okay. So, I guess, setting aside this type of curve then, how would you have created a fraction of the mass versus molecular weight graph, I guess if you can call it a curve --

A Yes.

Q -- your graph?

A Well, the -- the method we are talking about is completely different. This is creation of fractions you have in mind is a different approach to the measurement.

Previously we spoke about the gel permeation chromatograph, or gel chromatography, or size exclusion chromatography, where you are getting the curve as the output from the detector, okay.

Now, you appear to speak about doing different type of chromatography where you separate using very similar or identical mode, meaning, separation according to the size, but you don't run it through the detector. You run it in the individual [40] fractions or collect -- in individual glasses or something like that, and collect the fractions, okay.

And then you have fractions, but it tells you nothing about the molecular weight yet. Because the

next step must be the determination of the molecular weight of each of these fractions.

Q I see.

And how would you have done that?

A Well, you have to use, again, the gel chromatography or the size exclusion chromatography for each of these fractions, and you will get curves for each of them, and then from this, you would have to go back and put them all on the same -- on the same scale, and then you will see what you have.

And, essentially, the -- you don't get again any continuous curve, because you have a number of distribution curves, okay.

13. PAGE 41:15 TO 42:03 (RUNNING 00:00:40.750)

[41]

Q If you turn to paragraph 27 of your expert declaration, Dr. Svec, you have a paragraph that reads, "Moreover, because molecular weights of copolymers vary depending upon the measurement technique and the conditions used, the claims are further ambiguous"; do you see that?

A Yes.

Q Now, when you refer to the molecular weights depending upon the measurement technique in that paragraph, is that what you're referring to now, that there were various ways of measuring molecular [42] weights?

A Yes.

14. PAGE 42:04 TO 45:14 (RUNNING 00:04:53.016)

[42]

Q Can you tell me what -- in 1994 what those various ways of measuring molecular weight were?

A Certainly.

It could be light scattering, it could be use of membrane osmometry, it could be use of -- of centrifuge, it can perhaps be use of changes in the boiling point of liquids, just to name a few.

All these were known in the early 1990s.

Q Okay. I'm sorry to press you on this.

But other than the four that you just named, are you aware of any others that were available in 1994?

A Well, perhaps the degrees in the freezing point of solvents, you know.

Q When you refer to light scattering, is that also called MALLS?

A Yes, but I'm not sure that the -- the light scattering -- the MALLS scattering was available in that time.

Q Did you do any investigation, before you prepared your expert declaration, into whether MALLS was available in 1994?

[43]

A No, I did not.

Q Would it surprise you to learn that it was?

A Well, everything is possible.

Q It wouldn't surprise you to know that it was available in 1994; correct?

A Well, no.

Q It -- just to cut through, I'm not trying to hide the ball from you here, I'm just saying that you have a recollection that it became available some time in the mid-'90s, and you just don't remember exactly when; is that correct?

A Well, I know that the method exists, but I have no knowledge when it came up, when it has been used first for the characterization of polymers.

Q Okay. But it would not surprise you to know that it was available in 1994?

A No.

Q Okay. What about MALDI TOF? Do you know what that is?

A Yes, I do.

Q Can you explain for the court reporter, so we have it on the record, what MALDI TOF is?

A Well, you are using a plate that contains your sample mixed with a matrix. In fact, I should [44] say for the clarity, that "MALDI" means Matrix Assisted Laser-induced Desorption Ionization, that's MALDI.

And so you have the sample with the matrix mixed together. You put it in the equipment, and you hit it -- hit it with a laser beam at a wavelength of 315 nanometers. Typically, emanating from a nitrogen laser.

The energy of this beam evaporates the matrix, and the matrix takes with -- with it the sample, and then it is run through the mass spectrometer, and this determines the masses of -- of the individual molecules.

Q Masses are the molecular weights; correct?

A Well, this -- this -- this is molecular weight, of course.

Q Right.

In mass spec, it's actually molecular weight plus one; correct?

A Not always. It could be plus 13, you know.

Q Fair enough.

In a different kind of mass spec?

A Because you always have some -- some additional ions there, okay.

[45] So, for example, it can be the sodium ion that gives a little bit more on the wave, but we are aware of that, and so this is nothing we -- we do not know about.

Q MALDI TOF --

A "TOF" means Time Of Flight, okay. And if you have deionized molecules in the -- in the -- inside vacuum, they travel along -- they are accelerated, and then they travel, and the higher the molecular weight, the more -- the longer is the travel distance.

Q Was MALDI TOF available to measure molecular weight in 1994?

A I think it was.

15. PAGE 56:10 TO 57:04 (RUNNING 00:01:11.561)

[56]

MR. JAMES: Q. Dr. Svec, in your -- in the course of your career, and leading up to 1994, had you calculated number average molecular weight and weight average molecular weight using size exclusion chromatography data?

A Yes.

Q Okay. And do you have an understanding of the general relationship of those three values or of -- of those two values with peak molecular weight in polymer distribution curves?

A Well, I certainly have an understanding what is the relation between weight average and number average, but there is very little relation between these two and the peak molecular weight.

Q And why is that?

A Because the peak is just a value you read at [57] the top of the molecular weight distribution curve --

Q Okay.

A -- while the others have to be calculated.

16. PAGE 58:25 TO 59:08 (RUNNING 00:00:26.657)

[58]

Q Okay. And it's your testimony that people of [59] skill in your art at -- in 1994 -- or let me strike that.

It's your testimony that people of skill in the art of the '808 patent would not have had an understanding of the relationship between those three values; that is, number average molecular weight, peak molecular weight, and weight average molecular weight?

17. PAGE 59:11 TO 61:06 (RUNNING 00:01:59.274)

[59]

THE WITNESS: Well, do I understand well that you are asking me whether people skilled in the art in the 1994 knew that there are three different types of molecular weights available for characterization of polymers?

MR. JAMES: Let's start there.

Q Did they understand that?

A Probably, yes.

Q Okay. And did the people -- those people of skill in the art in 1994 have an understanding, based on their experience, like your experience, as to where on the molecular weight distribution curve the weight average would sit, the peak would sit, and the number average would sit?

A I think so.

[60]

Q Okay. And what is that understanding that they would have had in 1994 about those three values?

A I already told you that the -- the weight average molecular weight will be larger than the

number average molecular weight, and the peak molecular weight is unrelated, so it can be --

Q Okay. All right. I just want to make sure. So your -- your testimony is that you understand weight average would generally be larger than number average --

A That's right.

Q -- but that you don't have an understanding or you don't think that people of skill in the art in 1994 had an understanding as to how peak fit within those two values?

A That's not what I'm saying.

Q You're not?

A No, no.

Q Okay.

A What I'm saying is, that we have to be very careful about putting the peak molecular weight in the range of averages.

Q I see.

A Okay. So this -- this -- this is certainly [61] an issue, because the peak molecular weight is a single number, it's read from the curve, and it's unrelated to the weight average or number average, because it really depends on the shape of the curve only.

18. PAGE 63:05 TO 64:08 (RUNNING 00:01:04.004)

[63]

Q Okay. Are you aware of any molecular weight -- let me strike that.

Are you aware of any polymers that you've evaluated in your career where the distri- -- the distribution was that the number average molecular weight was greater than the weight average molecular weight?

A It can't be the case.

Q It can be?

A It can't be the case.

Q Okay. And what -- what sort of situation would that occur in?

A No, it -- it --

Q Oh, I'm sorry. It cannot be the case.

A It cannot be.

Q I did not understand what you said.

A No, no, no. Sorry. My English.

Q Mine, too.

A No, I think this -- this is -- this is impossible by default. Because in the, I would say, ideal situation, you have absolutely monodisperse [64] compound. The number average and weight average can be equal. Nothing -- nothing -- nothing else is possible.

Q Okay.

A Either the weight average is larger than the number average or, as I said, in a theoretical case, can be equal.

19. PAGE 67:07 TO 68:03 (RUNNING 00:01:25.030)

[67]

MR. JAMES: Okay. What are we up to? 4?

I'm going to mark as Svec Exhibit 4 a document that has a German title on the front, but the paper that I'm interested in asking Dr. Svec about is called "Monodisperse Polymer Beads as Packing Material for High-Performance Liquid Chromatography." It's from 1992, and it's authored by Dr. Svec, along with someone named Dr. Smigol, S-M-I-G-O-L, and others.

(Document marked Svec Exhibit 4 for identification.)

MR. JAMES: Q. Dr. Svec, if you could take a moment to look through that document, Svec 4, and tell me whether that is, in fact, an article that you published.

A Yes, it is.

Q And are you the author?

A Pardon?

Q Are you the author of this article?

A Yes, I was co-author of this article.

[68]

Q You participated in writing the article?

A Yes, I did.

20. PAGE 68:15 TO 70:20 (RUNNING 00:03:39.854)

[68]

MR. JAMES: Q. I think the pending question, Dr. Svec, is, can you tell me what the general subject matter of Svec 4 is?

A Okay. The general subject matter of this paper is development of monodisperse polymer beads that can be used as a stationary phase or, as we call it here, packing materials for high-performance liquid chromatography we discussed earlier today, and this is what we did.

We developed a method that enables the preparation of these polymer beads of having rather [69] uniform size, which is a little bit different approach than the general suspension polymerization we spoke about this morning as well.

Q And do I understand correctly that the paper primarily addresses the composition of the beads themselves, rather than their use?

A Yes, that's absolutely correct.

Q Okay. And there is discussion in this paper of the characteristics of the polymer that were -- that were -- that was used to make the beads; correct?

A Well, the beads are made by a process that you start from latex particles that are tiny. You swell them with a polymerization mixture under conditions that do not squalus, and then you initiate the theoretical polymerization that provides you with beads. And at the end of this process, you dissolve the original latex particles, in the case they are still

there, and you are getting material that can be used for HPLC.

Q So the latex beads are inside the polymer matrix?

A Well, it depends. In some cases, these beads remain inside of these particle -- I mean the beads.

Q Right.

[70]

A In some cases, and you would find it in my other papers, they are repelled from the particle during the polymerization process.

Q Okay. I'd like to ask you about the portion of the paper that appears on page 160. It's entitled "Molecular Weight of the Polymer Particles."

A Uh-huh.

Q Can you just, in general terms, tell me what is disclosed there on page 160?

A Well, since we are using these latex particles as the templates for the preparation of our porous polymers, we felt that it would be fair for those who will read this paper to see what was the -- what are the characteristics of those latex particles we used in our -- in our process.

It showed that there were two different latex particles used for this process. One that was based on polystyrene, while the other one was polymethylmethacrylate.

21. PAGE 70:21 TO 72:02 (RUNNING 00:01:49.169)

[70]

Q And the molecular weight distributions of the polystyrene and polymethylmethacrylate polymers are shown in Figure 4; correct?

A That's correct.

Q The top curve that says "PS" is the [71] polystyrene curve; is that correct?

A Yes.

Q And the bottom curve is polymethylmethacrylate, and it's labeled "PMMA"; correct?

A That's correct.

Q Now, the molecular distributions are graphed against a log scale of the molecular weight on the X axis; correct?

A That's correct.

Q What are the units on the Y axis? What do they refer to?

A The -- that's the -- what is the expression -- it's the fraction of molecules that have a specific molecular weight.

Q When you say "fraction of molecules," is that a weight fraction?

A No, that's a -- I don't think it's a weight fraction. It's -- in fact, you know, this is -- it --it's a -- a fraction of molecules can be everything. It can be

weight, it can be molar fraction, it can be even -- well, or -- or that -- that's it.

Q So the fraction can be weight or molar fraction?

[72]

A (Witness nods head.)

22. PAGE 73:13 TO 75:21 (RUNNING 00:03:12.750)

[73]

Q What if you needed to generate a curve like the ones shown in Figure 4 by hand?

A It can -- it -- I -- I don't think you can do that.

Q Why?

A Well, "by hand," what I -- I don't understand what do you mean, really, "by hand."

Q By taking the chromatogram and finding a -- a time point on the chromatogram, taking the weight as -- as evidence by the area.

A Oh, you mean the fractions?

Q Yes, the fractions.

A You're speaking about the fractions.

[74]

Q Well, I'm talking about integrating the chromatogram. Do you understand what that means?

A Yes.

Q Okay. Can you just say for the record what you understand that to mean, integrating the chromatogram?

A Yes. These curves are, what we would call, differential curves, okay. And if you calculate the area beneath this curve, it should be one, if it is in fractions, or 100 percent, 100.

If you want to see the individual weights of -- provided we are measuring weights -- the individual weights of each of these molecular weight -- at each molecular weight, I should say, then you probably would better like to work with the integral distribution curve, which would have a shape, which is kind of S-like shape, and then what you read from that is the amount of polymer molecules that have molecular weight up to a certain point, and the maximum where this curve goes is, again, 1 or 100 percent.

Q So at a specific time, you calculate the area within a rectangle that -- that's your integration, the width of your integrator, and you take that volume [75] as your weight of that -- particular molecular weight that you've picked somewhere within that rectangle; correct?

A (Witness nods head.)

Q And then you go up on your integration curve to the next molecular weight that you've picked and you create another tri- -- another rectangle; correct?

A I -- I -- I don't -- I don't think that this is how you create -- first of all, you cannot create any rectangles just out of nothing. You need to have either the fractions, as we discussed, meaning, you

have to separate the polymer in the individual fractions. Then you have to determine the molecular weight of these individual fractions, and then you can start creation of a -- not really curve, because you are getting individual points, you know.

Obviously, you can connect these points, but this is not what the experiment gives you. That experiment gives you the individual points.

Q Right.

23. PAGE 75:22 TO 75:24 (RUNNING 00:00:10.961)

[75]

A So you may see some shape, but the issue is that each of these fractions has its own distribution of the molecular weights.

24. PAGE 76:03 TO 76:13 (RUNNING 00:00:37.416)

[76]

Q Now, you mentioned that's one way, is that you take the fractions and you measure their molecular weights and then you graph the percentage of each of those molecular weights, and then you're saying you get a set of points, and then you could connect them with a curve, but -- or not?

A Well, you can connect them with a curve, but the curve has no experimental meaning. This is just to make it nice, but it certainly does not have any scientific background for -- for that. Generally, it's not supported by any data in all the curve.

25. PAGE 77:03 TO 77:05 (RUNNING 00:00:11.676)

[77]

Q -- could you use a molecular weight calibration curve in order to graph the percentage of polymer at each molecular weight?

26. PAGE 77:07 TO 77:15 (RUNNING 00:00:37.612)

[77]

THE WITNESS: You -- I -- I don't think you can do this, because what you need to do is to use the calibration curve to translate the elution times into a molecular weight, and that's all you can do with the calibration curve, you know.

You cannot use the calibration curve to -- to create and integrate the integral -- integral ¬integral molecular weight distribution curve or molecular distribution shape.

27. PAGE 77:16 TO 80:21 (RUNNING 00:05:06.710)

[77]

MR. JAMES: Q. You're saying you cannot use the calibration curve, along with the integral curve, in order to determine the percent of --

A No, no.

Q -- each molecular weight?

A No, no, no. That's not what I'm saying.

What I'm saying is, that you cannot use the calibration to create an integral molecular weight distribution curve, you know.

You need to have some experimental data [78] that you use to create the curve. The experimental data are translated to the molecular weight using the calibration, and then you can perhaps create the molecular weight distribution curve.

Q You said you need to have some experimental data that you use to create the curve.

What curve are you --

A Well, I --

Q -- meaning in that -- in that answer?

A Well, again, I think I am mixing things.

Q Me too, okay, so --

A I'm -- what I mean is, again, we are not -- I certainly said several times, that using fractions, we are not creating a curve. We are creating a shape, let's say, okay, because we have only a few or certain point of experimental points.

We can connect them, and I said it does not have any real scientific meaning, because most of the curve is not substantiated by any experiments, okay.

Still, we are using words, "curve," but I would like to make sure that this is not completely correct, you know. So that's probably the explanation why I used the word "curve," although it was not really absolutely correct.

[79]

Q Going back to that sentence that you used earlier, you said you need to have some experimental data that you used to create the curve, and I think what you've done is explain what you meant by curve is the shape, which would be the shape of the data points of the percent at each molecular weight that you've measured.

A Well, each -- you certainly -- again, you don't -- you don't specify what is the molecular weight we measured. We did not specify, I have to say.

So obviously the curves we are talking about, you know, they can show perhaps the peak molecular weights of each fraction, and you will get one shape, and from that you will see or you will get an idea about the shape of these -- these individual points.

You can certainly do similar calculation -¬or you can do some calculations and get it done for the other types of...

Q Okay. If you create that shape of the weight percent versus the molecular weight of -- showing the distribution, if you will, of a particular polymer sample, can you then use that to create -- calculate the number average and weight average molecular [80] weight?

A If you have the shape only --

Q Yes.

A -- from the points?

That might be difficult, because it can be -¬it can be -- let me think.

If you have a shape of the distribution curve, then you know what are the individual points, and you

can use the mathematical expressions for the calculation of the weight and number averages.

Q Okay. Using the shape that we mentioned a moment ago, percentage of weight versus molecular weight, can you read the peak molecular weight?

A Of the overall polymer --

Q Yes.

A -- from the individual fractions?

Q Yes.

A Depends how many individual points you have, you know, because you can miss certainly the apex of -- you know, it depends where you are with those.

28. PAGE 86:02 TO 86:07 (RUNNING 00:00:23.991)

[86]

Q And because it's not as narrow a rectangle as you are measuring with the UV detector, when you transfer it to this percentage weight versus molecular weight curve, all I'm asking you is, can the peak be shifted because of the imprecise nature of the integration?

29. PAGE 86:09 TO 87:09 (RUNNING 00:01:31.891)

[86]

THE WITNESS: I -- I don't think so. This -¬this -- you know, the -- the creation of the shape is given by the number of fractions and the molecular weight of each of these fractions, and from that you can

certainly create the integral -- the differential curves, and you can integrate these differential curves to get the integral curves, you know.

MR. JAMES: But -- sorry.

THE WITNESS: And, again, you -- the shift may not be -- may not be just because of any imperfection of -- of your measurement, you know.

The measurement is as perfect as you can get it, and my impression is that we -- we don't have the liberty to -- to move things one way or the other way just blaming the imperfection of measurements.

MR. JAMES: Q. You know, I'm not saying [87] blaming the imperfection of measurements. I'm saying that in -- if you were doing -- I'm just asking you if you were going to do a manual integration and create this shape of weight percentage versus molecular weight, as a function of not purposefully moving the peak, but the imperfections of math, if you will, that the peak on your shape could be shifted to a slightly different molecular weight value than that read off of the chromatogram?

30. PAGE 87:11 TO 87:16 (RUNNING 00:00:08.886)

[87]

THE WITNESS: I -- I don't think so, no.

This -- this -- this may not be the case.

MR. JAMES: Q. It can't happened?

A It can't happen.

Q Cannot happen?

A (Witness shakes head.)

31. PAGE 92:20 TO 94:02 (RUNNING 00:02:05.550)

[92]

MR. JAMES: Q. In 1994, you mentioned that a person of skill in the art would have understood the concept of column calibration --

A Yes.

Q -- correct?

Does column calibration take into account [93] the idea of hydrodynamic volume?

A That's right.

Q Can you explain how?

A Well, size exclusion chromatography does not separate, really, based on molecular weight. It separates on the differences in the hydrodynamic size of the mole- -- molecules; and, fortunately, the hydrodynamic size of molecules depends on properties that we may use for the calibration, you know.

So there is a relationship between the viscosity of the molecules and molecular weight at -- in -- in a specific solvent, because the solvent plays a significant role in -- in solvation of the molecules we are measuring, and based on the extent of solvation, the hydrodynamic size changes, okay, and the solvation depends on the character of that specific molecule, you know.

You may have molecules that like the solvent very much and other molecules may not like them at all, you know. So this is what happened.

Q And, in general, when you're calibrating your curve, is it important to use calibration standards that have a similar hydrodynamic volume or at least a similar relationship between hydrodynamic volume and [94] molecular weight to the sample that you're measuring?

32. PAGE 94:04 TO 95:20 (RUNNING 00:02:34.680)

[94]

THE WITNESS: Not really, because there is something called universal calibration, which is very often used in the measurements.

MR. JAMES: Q. What is universal calibration?

A That's a calibration with a calibrant that eventually can -- we know the properties and we can do the mathematics calculation of the universal calibration curve. But certainly, if you -- if you want to use this for a separation or for a determination of the molecular weight, you better use calibrants that are really close to the chemistry of those compounds, which is sometimes very difficult to achieve simply because the standards may not be available.

Q So you're saying if -- let me make sure I understand your answer.

You're saying if you don't use the universal calibration, that it's important to use standards that are close in their chemistry to the sample that you're measuring; is that correct?

A I'm saying -- what I'm saying is that you [95] have two options. One option is to use the universal calibration. The other option is to use calibration with standards that are close to -- to what you are measuring.

Q And what do you mean by "close"? What characteristics would be important in being close?

A Well -- so, for example, if you measure your molecular weight in aqueous solutions, certainly the calibrants has to be soluble in water, you know. So this is -- this is one of the conditions.

Q Anything else?

A Well, the chemistry should probably be similar.

Q What do you mean by "the chemistry"?

A Well, I mean, that if you try to use or try to separate saccharides, you probably use the polydextrans as calibrants, because this is similar chemistry of the calibrant and these -- these polymeric sugars.

33. PAGE 95:21 TO 95:25 (RUNNING 00:00:21.397)

[95]

Q And if you're separating polypeptides, what would you use as the standards?

A Probably, I would use proteins.

Q Why would you use proteins?

A Because they have similar chemical structure.

34. PAGE 97:25 TO 98:05 (RUNNING 00:00:13.991)

[97]

Q In 1994, would a person of skill in the art [98] have understood that in order to get the most accurate molecular weight measurement possible, that the best standard would be a standard of the sample they were actually measuring?

35. PAGE 98:16 TO 98:22 (RUNNING 00:00:31.748)

[98]

A Okay. Well, probably this would be the case that the polypeptides would be quite good standards for the characterization. The issue is how do you gather them.

Q And in 1994, was there any way to gather samples of the polypeptides that you wanted to measure in order to create standards?

36. PAGE 98:24 TO 99:04 (RUNNING 00:00:25.930)

[98]

THE WITNESS: You would probably have to synthesize them. The technology, in 1994, for the [99] preparation of specific peptides was already available, so you could probably get peptides in a specific length, would be certainly possible.

37. PAGE 99:05 TO 99:10 (RUNNING 00:00:21.750)

[99]

MR. JAMES: Q. In 1994, in order to measure the molecular weights -- the molecular weight distribution of a polypeptide sample, could you have taken small fractions of the sample and determined the molecular weight of those fractions in order to use them as standards?

38. PAGE 99:12 TO 99:21 (RUNNING 00:00:32.680)

[99]

THE WITNESS: I don't -- I don't see any good reason to doing that, because it would -- if you extend this any farther, then we will get -- we will essentially take an unknown, we will cut it down to small fractions, and then use them in a circular way for characterization of -- of the complete polymer.

MR. JAMES: Q. And -- and, yeah, characterize it in terms of its molecular weight distribution, yes. I'm asking you whether you could have done that.

39. PAGE 99:23 TO 99:24 (RUNNING 00:00:03.013)

[99]

THE WITNESS: I -- I don't think this is the way to go.

40. PAGE 100:05 TO 100:10 (RUNNING 00:00:16.966)

[100]

Q I'm just asking you, in 1994, was the technology available to the person of skill in the art to do that; that is, take the unknown sample, take fractions of the sample, determine the molecular weight of those fractions or some of those fractions, and calibrate the column?

41. PAGE 100:12 TO 101:02 (RUNNING 00:01:00.534)

[100]

THE WITNESS: Let me think.

If you create the narrower molecular weight of fractions of a polymer -- of a polypeptide, you characterize them, and then you use them for calibration of your measurement; that's what you are asking?

MR. JAMES: Yes, sir.

THE WITNESS: Yeah.

So then -- and you characterize them, I think I said that already. So you probably can get a system that may help you in the characterization of the overall molecular weight.

MR. JAMES: Q. You could -- you could generate a molecular weight distribution for the [101] unknown; correct?

42. PAGE 101:04 TO 101:10 (RUNNING 00:00:13.646)

[101]

THE WITNESS: We are -- we are back again at square one, because we already discussed the issue that if you have molecular weights of the individual fractions

MR. JAMES: Yes.

THE WITNESS: -- then you can create the individual points on the distribution curve.

43. PAGE 101:12 TO 102:02 (RUNNING 00:00:30.992)

[101]

Q I -- I'm just asking you a slightly different question, which is that you could take the fractions, and I think you already said that you could determine the molecular weight of those fractions --

A Uh-huh.

Q -- and if you took a small enough fraction, it would be relatively narrow; correct?

A Yes.

Q And then if you have those molecular weights of those fractions and you put them into your column to see where they elute, that you could create a molecular weight calibration curve for your column --

A Yes.

Q -- for that unknown; correct?

[102]

A That's right.

44. PAGE 107:04 TO 107:09 (RUNNING 00:00:15.328)

[107]

Q And the importance of having hydrodynamic volumes that were properly correlated with the molecular weight of the sample, that was a concept that was understood in 1994 –

A Yes.

Q -- correct?

45. PAGE 130:21 TO 130:24 (RUNNING 00:00:14.746)

[130]

Q Is it your opinion that all of the claim terms refer to average molecular weight?

A No, I -- I -- I don't think that the claims are referring to average molecular weight.

46. PAGE 130:25 TO 131:12 (RUNNING 00:00:40.750)

[130]

Q Okay. So why would the claims be indefinite [131] because it -- the claims that don't refer to average molecular weight, why would they be indefinite because, in your opinion, the patent doesn't teach you how to calculate average molecular weight?

A Well, simply, the molecular weight shown in the patent doesn't say what type of molecular weight it is. So from that point, we don't know, really, what

the patent is talking about, simply because there is no specification of the molecular weight in question, and, therefore, from that point of view, it's completely indefinite.

47. PAGE 132:08 TO 132:17 (RUNNING 00:00:18.211)

[132]

Q And do you understand what "species of copolymer-1" means?

A Yeah, I think so.

Q What's that?

A That's the individual molecules in the sample.

Q The individual molecules in the copolymer-1 sample, and each of those would have a molecular weight; correct?

A Yes, it has to have a molecular weight.

48. PAGE 132:18 TO 132:22 (RUNNING 00:00:23.159)

[132]

Q And so when it says that the -- it's free of species of copolymer-1 having a molecular weight of over 40-kilodaltons, that means that there are it's substantially free of individual molecules that have a molecular weight over 40-kilodaltons; correct?

49. PAGE 132:25 TO 133:06 (RUNNING 00:00:26.908)

[132]

THE WITNESS: Well, again, this -- your – [133] your wording is a little bit misleading, because we

don't know what is 40-kilodaltons. Is that molecular weight at a certain point of the curve, or is that a -- an average molecular weight that is calculated? I don't know.

50. PAGE 133:13 TO 133:22 (RUNNING 00:00:32.276)

[133]

Q Okay. And so here, in this sentence that you've referred me to, when it talks about species or a specie of copolymer-1 having a molecular weight over 40 kilodaltons, "molecular weight" there refers to the -- the sum of the atomic weights of the atoms in that species; correct?

A Yes.

Q So there's -- there's no average molecular weight phrase in that sentence; correct?

A No.

51. PAGE 133:23 TO 134:02 (RUNNING 00:00:13.910)

[133]

Q So the -- the -- really, that sentence indicates that the person of skill in the art has to determine whether there are species having a molecular [134] weight over 40 kilodaltons; right?

52. PAGE 134:04 TO 134:15 (RUNNING 00:00:50.062)

[134]

THE WITNESS: Well, my understanding, if I interpret it using my own knowledge, well, the 40

kilodaltons here must mean a certain point or certain limit, which certainly is a limit, and the limit has to be defined, you know. 40,000, well, it doesn't say anything about single species, you know. It says "of species," plural.

MR. JAMES: Q. But that means a collection of individual species; correct?

A Okay. Yes.

So my impression is that this -- this is -¬this is less defined than I would expect.

53. PAGE 134:16 TO 134:20 (RUNNING 00:00:14.525)

[134]

Q Dr. Svec, if someone provided you with a sample of copolymer-1 and asked you to determine what the percentage of species having a molecular weight above 40 kilodaltons was, would you be able to do that?

54. PAGE 134:22 TO 135:07 (RUNNING 00:00:29.156)

[134]

THE WITNESS: Well, if somebody gives me a sample, how could I know that the sample is based on -- on the patent?

MR. JAMES: Q. Well, they're saying that [135] I -- I made it, as you make copolymer-1, using the correct amino acids and the correct ratio. And they -- they tell you that it's copolymer-1, so I'm asking you, would you be able to determine the number or

percentage of species of copolymer-1 having a molecular weight over 40 kilodaltons?

55. PAGE 135:09 TO 135:21 (RUNNING 00:00:52.561)

[135]

THE WITNESS: Well, if I get a sample like this, there are methods available that can enable determination of molecular weight and probably molecular weight distribution, because that's where the problem stems. And if you would get the molecular weight distribution curve, we can certainly look at that and see how the molecular weight distribution curve -- curve looks like, you know.

That -- that's -- that's the answer.

MR. JAMES: Q. Isn't it true that if you have that distribution curve, that you can then ask the computer to tell you what the percentage of species that have a molecular weight above 40 is?

56. PAGE 136:08 TO 136:13 (RUNNING 00:00:18.908)

[136]

Q The question on the table is, the patent talks about percentage of species with a molecular weight above 40 kilodaltons, and that means -- in that context, molecular weight means the sum of the atomic weights of that species; correct?

A Yes.

57. PAGE 136:15 TO 136:18 (RUNNING 00:00:13.274)

[136]

MR. JAMES: Q. And so all we have to determine is whether a person of skill in the art would be able to determine the percentage of those species that fall above 40 kilodaltons.

58. PAGE 136:20 TO 137:08 (RUNNING 00:00:33.372)

[136]

THE WITNESS: Well, technically, this is quite difficult, you know.

MR. JAMES: Okay.

Q Can you tell me why it's difficult?

A Because you don't -- you -- you don't have the means to go for each individual species in the [137] sample. You know, it's -- it's -- they are not methods that allow you to pick up one and measure whether or not it has 40,000 molecular weight or not and throw it one way or the other, you know.

So from that point of view, of course, it's -- it's not that easy, you know. It's not possible.

59. PAGE 137:21 TO 138:20 (RUNNING 00:01:32.216)

[137]

If you have a calibration curve, you can know how many species are above 40 kilodaltons; correct?

A Well, you -- yes, you -- you have to translate the curve you got from your UV detector into the molecular weights. That's what you said.

[138]

Q The distribution curve?

A To get –

Q Right.

A -- the molecular weight distribution curve, and the -- the -- and you can assume that there is a point 40,000 dalton, which shows how many of these species might be above or not.

The problem, though, is that in the calibration, you know, because you don't calibrate each individual species in the system, and, therefore, the -- the curve certainly shows some kind of trend, but how it is really -- you know, you never get a single species at a single time, you know. The curve is not done this way.

You always have several species coming out at each certain time, and, therefore, it would be -¬it -- it -- it can be done on paper, but in reality, you will never get species that are over 40,000 separated from those that are less than 40,000.

60. PAGE 140:08 TO 141:13 (RUNNING 00:02:03.133)

[140]

MR. JAMES: Q. Dr. Svec, if you could look at the summary of the invention in the '808 patent, it's in Column 1, starts at about line 42 or so, the first paragraph says, "The present invention relates to a

composition of copolymer-1, substantially free of species of copolymer-1, having a molecular weight of over 40 kilodaltons"; do you see that?

[141]

A Yes.

Q And you and I, we discussed that same concept, a molecular weight over 40-kilodaltons, in ¬in the context of the detailed description; correct?

A Yes.

Q And then, if you look at the next paragraph, it says, "The invention further relates to a copolymer-1 having over 75 percent of its molar fraction within the molecular weight range from about 2 kilodaltons to about 20 kilodaltons"; do you see that?

A Yes.

Q Now, is it your -- let me strike that.

What do you understand "molecular weight range" to mean in that paragraph?

A Well, I understand that it defines limits of a molecular weight.

Q So it is indicating that there is a percentage of the total sample where those individual copolymers in that percentage -- there's a percentage made up of individual copolymers that have individual molecular weights that are greater than about 2 and less than about 20; correct?

61. PAGE 141:15 TO 141:25 (RUNNING 00:00:27.819)

[141]

MR. JAMES: Q. Is that correct?

A It seems to be correct, yeah.

Q Okay. And in that context, that molecular weight range, is that referring to an average molecular weight?

A I don't know.

Q Okay. You -- you can't tell?

A It doesn't say anything like that.

Q Okay. It doesn't say average molecular weight?

A Doesn't say anything.

62. PAGE 142:02 TO 142:12 (RUNNING 00:00:28.145)

[142]

Q Okay. And then, in the next paragraph, it says, "In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 kilodaltons"; do you see that?

A Uh-huh, yes.

Q And, obviously, that phrase, "average molecular weight," is something we've talked a lot about today, and -- but -- in -- well, I guess, the question I had was, in these three paragraphs, the term "molecular weight" is used in different ways; correct?

63. PAGE 142:14 TO 143:09 (RUNNING 00:01:07.389)

[142]

MR. JAMES: Q. In the first paragraph, it refers to species that have individual molecular weights, where it says "a molecular weight of over 40 kilodaltons"; correct?

A Yes.

Q And in the second paragraph of the summary, it refers to percentage of copolymers that have individual molecular weights that are greater than about 2 and less than about 20; correct?

A Yes.

Q And then, in the last paragraph, it refers to average molecular weights; right?

[143]

A Yes. Well, what I see here is a problem, because you cannot have an average molecular weight that has a range, because molecular weight is one thing -- I mean, the average molecular weight is a single number.

Q So doesn't that indicate that the average molecular weight number is between about 4 and about 8.6 kilodaltons?

64. PAGE 143:11 TO 143:19 (RUNNING 00:00:25.590)

[143]

THE WITNESS: I don't see it that way. MR. JAMES:

Q. You don't?

A (Witness shakes head.)

Q Okay. So if someone brought you a sample and they said, "It's copolymer-1, Dr. Svec. Can you determine whether it has an average molecular weight of about 4 -- between about 4 and about 8.6," you wouldn't know how to do that?

A Yes; I won't.

65. PAGE 146:02 TO 146:10 (RUNNING 00:00:24.956)

[146]

MR. JAMES: Q. Dr. Svec, in 1994, if someone had given you an example of co- -- copolymer-1, would you have been able to determine whether it had an average molecular weight between 5,000 and 9,000 kilodaltons?

A What average molecular weight?

Q Okay. Would you have been able to determine whether it had a peak molecular weight between 5,000 and 9,000 kilodaltons?

66. PAGE 146:12 TO 146:16 (RUNNING 00:00:13.589)

[146]

THE WITNESS: Probably, yes, yes.

MR. JAMES: Q. And you would have been able to determine that by determining that the molecular weight at the peak of the chromatogram was -- fell between 5,000 and 9,000; correct?

67. PAGE 146:18 TO 146:22 (RUNNING 00:00:17.286)

[146]

THE WITNESS: Well, you -- if you have the molecular weight distribution curve, you can determine the apex of the molecular -- the molecular weight distribution curve and get an idea about the peak molecular weight.

68. PAGE 163.18 TO 164:03 (RUNNING 00:00:31.143)

[163]

Q Do you understand that, when you're interpreting a patent, that a person of skill in the art is assumed to have access and knowledge of all of the prior art that comes before that patent? Do you understand that?

A I'm not getting the question.

Q In other words, the person of skill in the art has the background/knowledge of how to do size exclusion chromatography, how to calibrate a size exclusion column; okay?

69. PAGE 164:05 TO 164:16 (RUNNING 00:00:43.397)

[164]

MR. JAMES: Q. So do you -- did you understand that when you rendered your opinion that the person of skill in the art was assumed to come to the patent with that knowledge?

A I understood that some -- somebody who came up to the knowledge of the patent issues in 1994 may

understand how the size exclusion chromatography is being done, because that's the open literature and everybody can read it and probably this is what is being taught at the universities, and so, from that point of view, I think that whoever came up -- came to the patent had this background/knowledge.

70. PAGE 165:02 TO 166:04 (RUNNING 00:01:01.286)

[165]

A Yes.

Q I just want to make sure I understand the basis for your opinions.

When you rendered your opinions, did you understand that the person of skill in the art would have knowledge of the prior art when they were interpreting the patent?

A Well, again, depends on the definition of "prior art," you know.

Q Everything that came before the patent.

A Yes, what I said is that I read this patent knowing what -- you can call it prior art -- what the method is all about, how you use size exclusion chromatography.

Q Okay. A person of skill in the art would understand how to use size exclusion chromatography; correct?

A Yes.

Q A person of skill in the art would understand how to calibrate a column; correct?

A Yes.

Q A person of skill in the art would understand the importance of getting the hydrodynamic volume of the standards they used correct with -- with respect [166] to the sample that they're measuring; isn't that right?

A Yes.

71. PAGE 172:07 TO 172:11 (RUNNING 00:00:11.917)

[172]

Q When it says that no copolymer-1 species present in this batch had a molecular weight over 40-kilodaltons, that's referring to an individual molecular weight, meaning, the sum of the atomic weights; correct?

72. PAGE 172:13 TO 173:03 (RUNNING 00:01:03.129)

[172]

THE WITNESS: Well, I -- this method does not allow you to do this, you know, because this is just a we -- we discussed this issue previously.

So in this case, you don't get anything that can tell you that they -- there are no individual species over the 40,000 dalton molecular weight, because here you are creating a distribution curve, and, in fact, we don't even know whether or not there was a distribution curve created, because it doesn't say anything about -- about how they would do this, and they'll ask, then, what is the average molecular weight.

There are several types of averages, and this [173] doesn't say anything about which one are they talking about.

73. PAGE 194:23 TO 195:02 (RUNNING 00:00:17.000)

[194]

Q Do you know what a molar fraction is?

A Yes. That's the number of moles of a specific species, divided by the order number of moles [195] of -- of all species in the sample.

74. PAGE 195:24 TO 196:09 (RUNNING 00:00:16.402)

[195]

Q Right.

All I'm asking you is, every mole contains [196] the same number of molecules?

A That's right, yeah. That's the Avogadro number.

Q Right.

So if you take out Avogadro's number, mole fraction is the number of molecules of a species over the total number of molecules in the sample?

A Yes.

75. PAGE 245:04 TO 245:10 (RUNNING 00:00:21.750)

[245]

Q Now, the peak molecular weight comes right off the chromatogram; correct?

A Not -- not really, because out of the chromatogram comes the elution time, you know, so you cannot say immediately that this is the peak molecular weight -- the peak of curve that goes out of the system.

76. PAGE 245:12 TO 246:06 (RUNNING 00:01:01.455)

[245]

If you have a calibrated column, you can read the molecular weight off of the chromatogram; correct?

A If you have a calibrated column with the elution volumes trans- -- transferred to -- to molecular weights, then you can do what we did here with the Figure 1 and Figure 2, and see what the ¬the peak molecular weight could be.

Q Okay. So in that sense, this size exclusion chromatography technique will give you the peak molecular weight?

A It will give you peak molecular weight, weight average molecular weight, and number average molecular weight, if done properly.

Q Okay. Now, how does the size exclusion [246] chromatography technique give you a number average and a weight average molecular weight?

A Well, this does not give you these values directly. You have to calculate them from -- from the -- from the curve.

77. PAGE 247:04 TO 247:09 (RUNNING 00:00:06.500)

[247]

Q You can calculate the number average and weight average ¬

A Yes.

Q -- and you have the peak molecular weight; correct?

A That's right.

78. PAGE 251:15 TO 252:09 (RUNNING 00:00:45.635)

[251]

Q I'm just saying, you don't have any reason to -- to -- all I'm saying is that the patentees told the examiner that average molecular weight means peak molecular weight; right?

A Yeah, that's right.

Q And you have no reason to doubt what they said; correct?

A I do. I do have a reason, because, as I said already, there is no evidence for the fact that the molecular weight as set is the peak molecular weight.

Q Okay. You believe that average molecular [252] weight can't be interpreted because it could mean multiple things; correct?

A That's what I'm saying.

Q Right.

A It's —

Q But as a factual matter, you have no reason, sitting here today, to doubt that, in fact, average molecular weight meant peak molecular weight –

79. PAGE 252:11 TO 253:03 (RUNNING 00:01:02.627)

[252]

MR. JAMES: Q. -- correct?

A What I'm saying, and we are playing with this, is that I -- I do have reason to believe that this is not the peak molecular weight, because there is no evidence that this is the molecular -- the ¬the peak molecular weight, even looking at it.

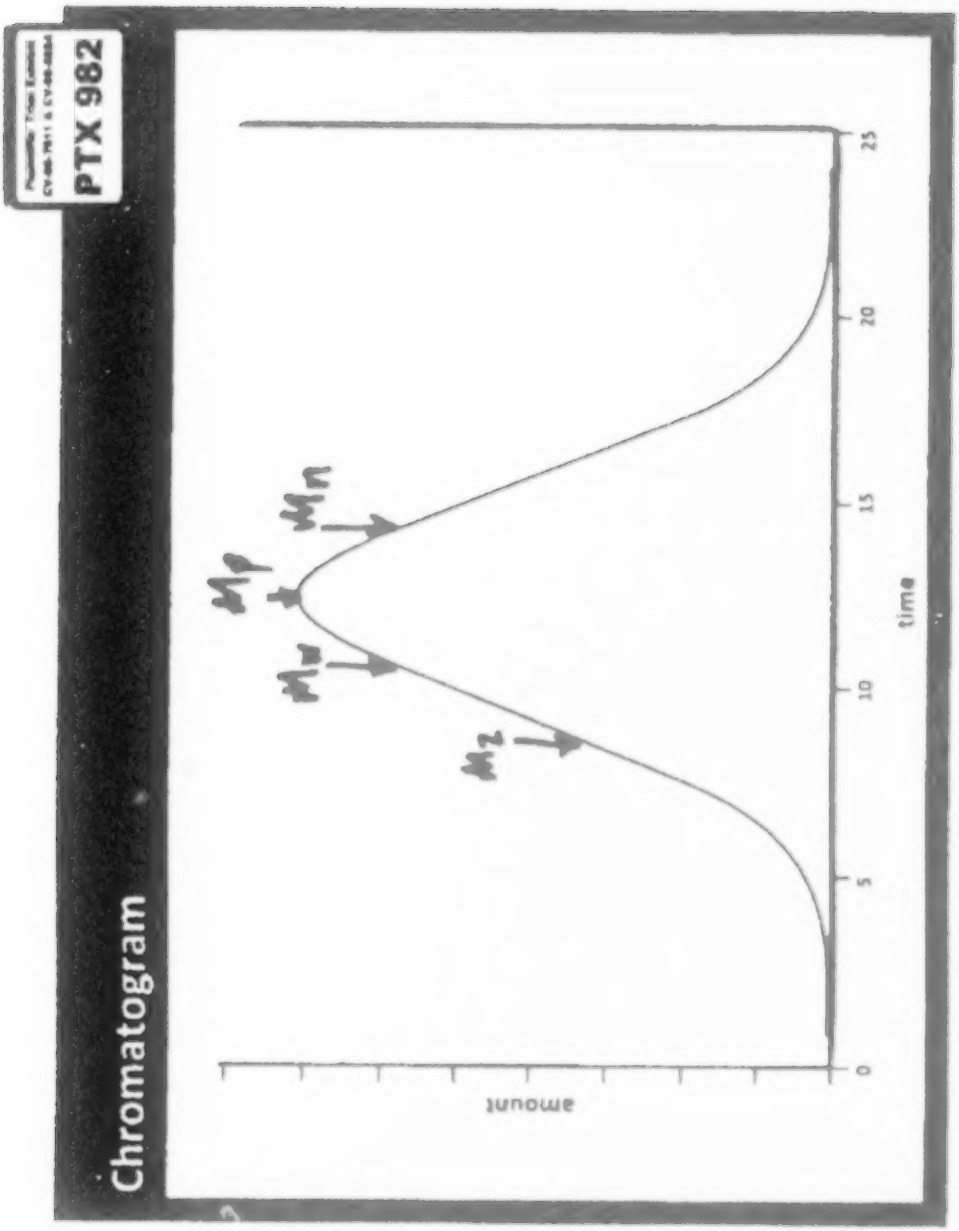
Q Okay. And what is your reason to doubt that it is, in fact, the peak molecular weight that's listed in that legend of Figure 1?

A Well, we demonstrated by the measurements that we did, that the peak molecular weight is different from the -- the molecular weight stated in the patent.

Q And the fact that it's different leads you to believe that it can't be the peak molecular weight?

[253]

A It -- I -- it leads me to the fact that we don't know.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TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD.
Plaintiffs,
v.
SANDOZ, INC. and MOMENTA PHARMACEUTICALS, INC.,
Defendants.
Civil Action No. 08-CV-7611 (BSJ)(AJP)

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD.
Plaintiffs,
v.
MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD.
Defendants.
Civil Action No. 09-CV-8824 (BSJ)(AJP)

Gregory Grant, Ph.D.

September 7, 2011

Overview

- Background on Technology of Patents-in-Suit
  - Copolymer-1
  - Size Exclusion Chromatography (SEC)
- Application of Claims to Defendants' ANDA Products
  - Comparison of the ANDA products with the molecular weight claim terms

Level of Skill in the Art

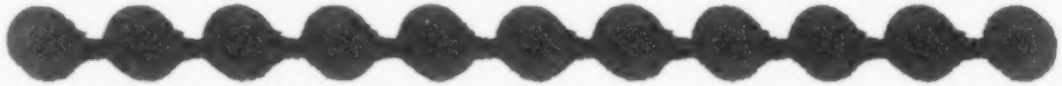
Qualifications of a person of skill:

- **Advanced degree or equivalent in a chemical or biological discipline, and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides**
- **Access to and the ability to consult with other scientists having related and/or complementary knowledge and experience in the areas of polymer chemistry, biochemistry, analytical chemistry, separation technology, medicine, and toxicology**

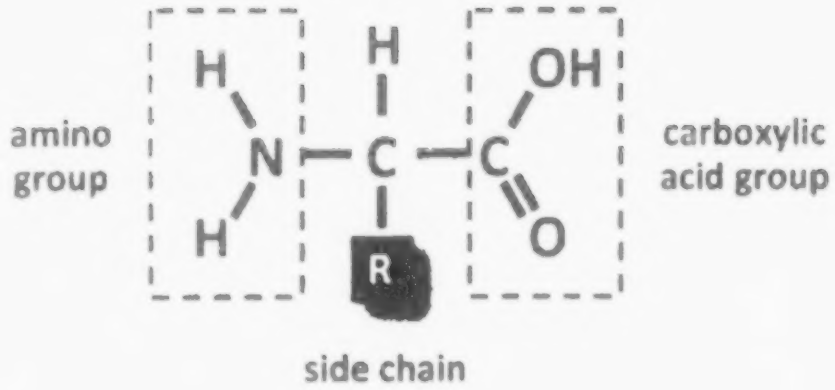
Polymer, Copolymer

A **polymer** is a molecule composed of **monomers**

A **copolymer** is a polymer composed of more than one type of **monomer**



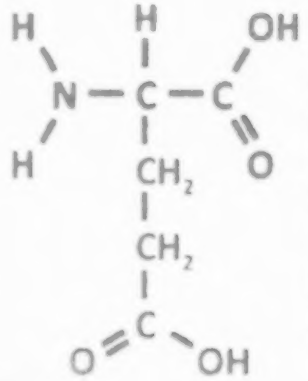
Amino Acid



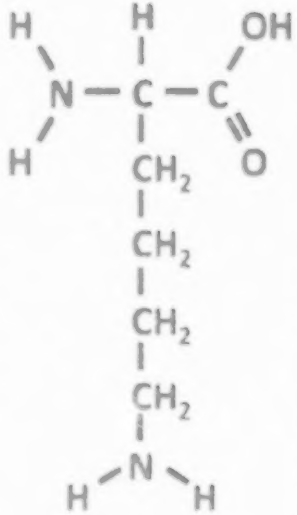
5

Amino Acids in Copolymer-1

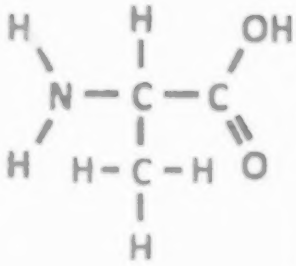
glutamic acid



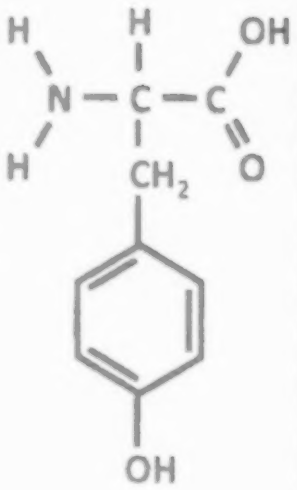
lysine



alanine



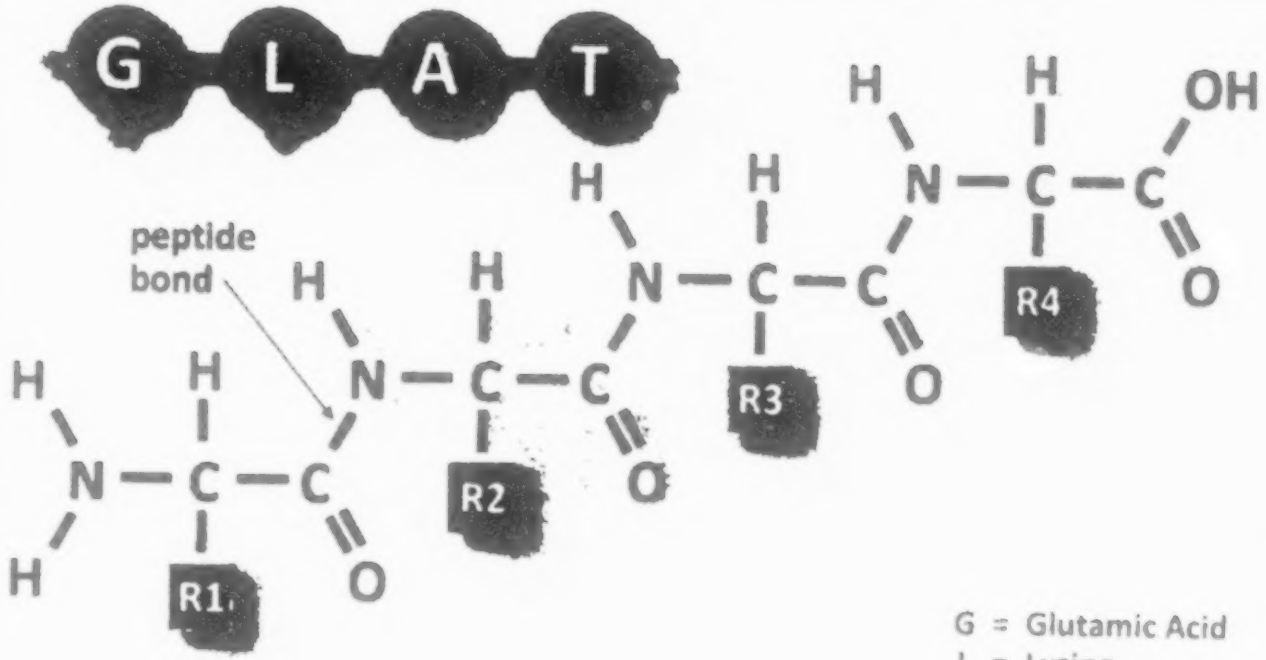
tyrosine



G L A T

6

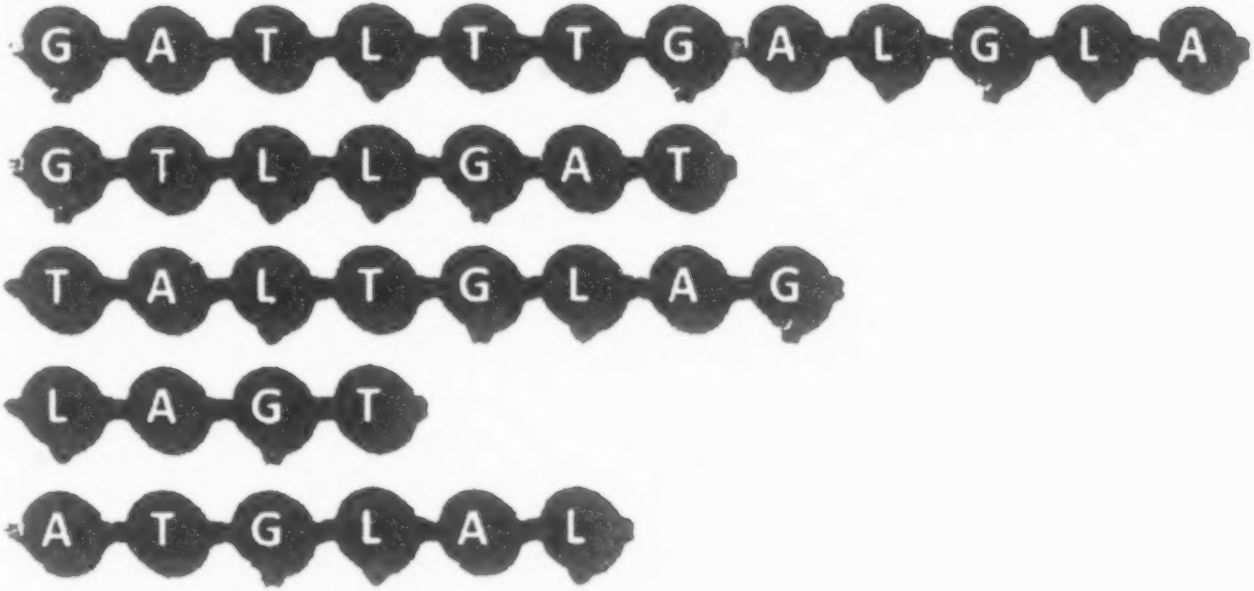
Copolymer-1 Polypeptide



7

800a

Copolymer-1 Polypeptides Differ in Length and Sequence

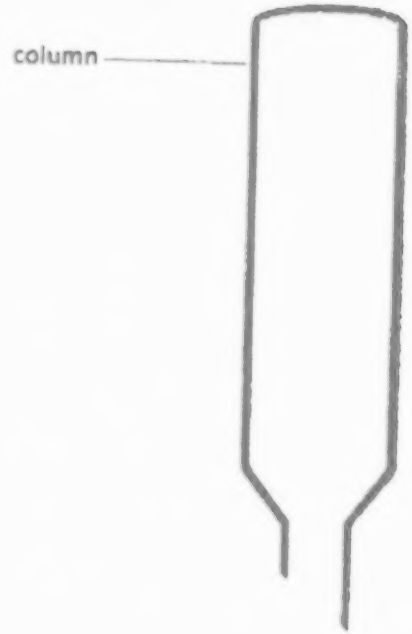


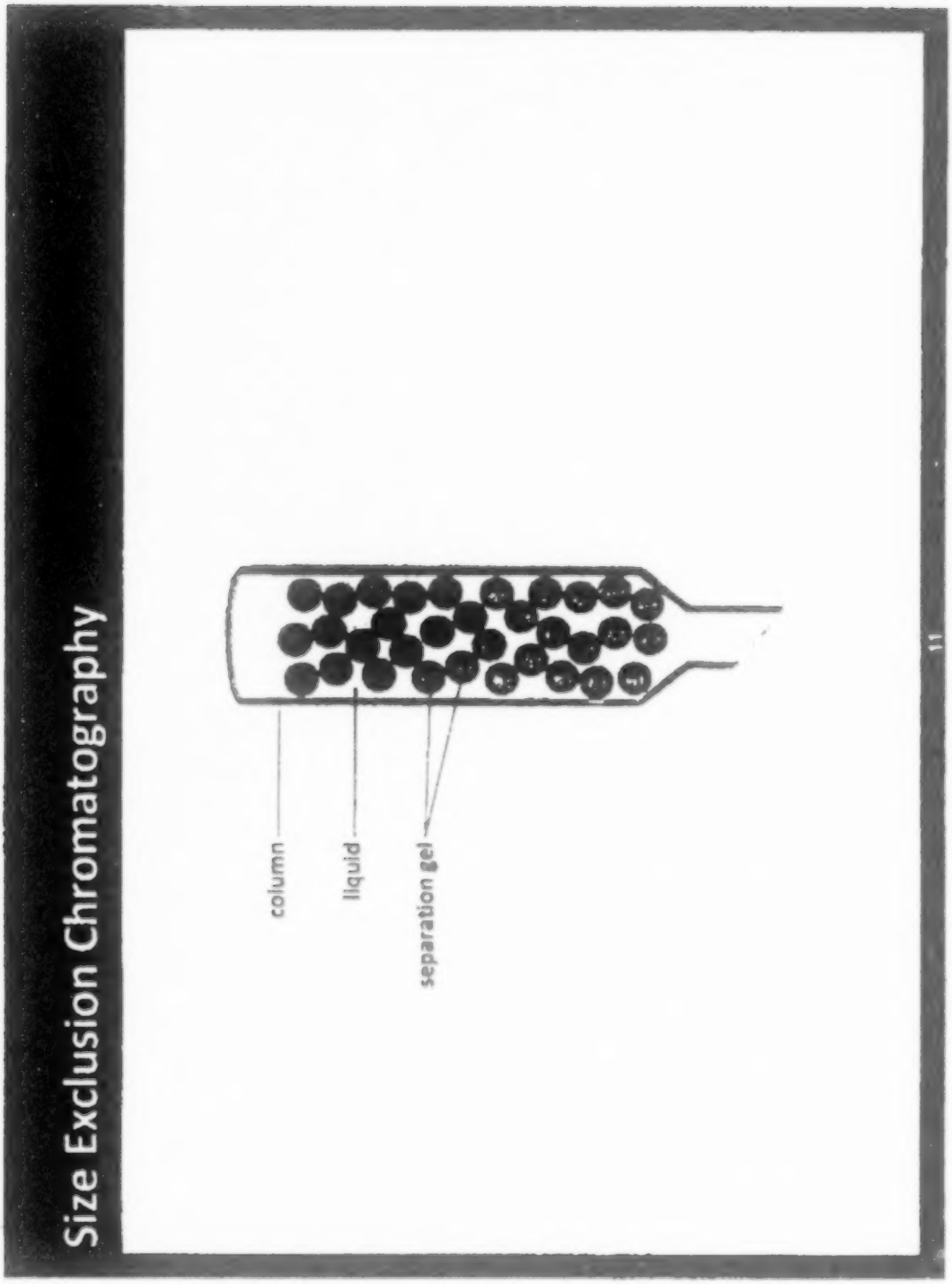
G = Glutamic Acid
L = Lysine
A = Alanine
T = Tyrosine

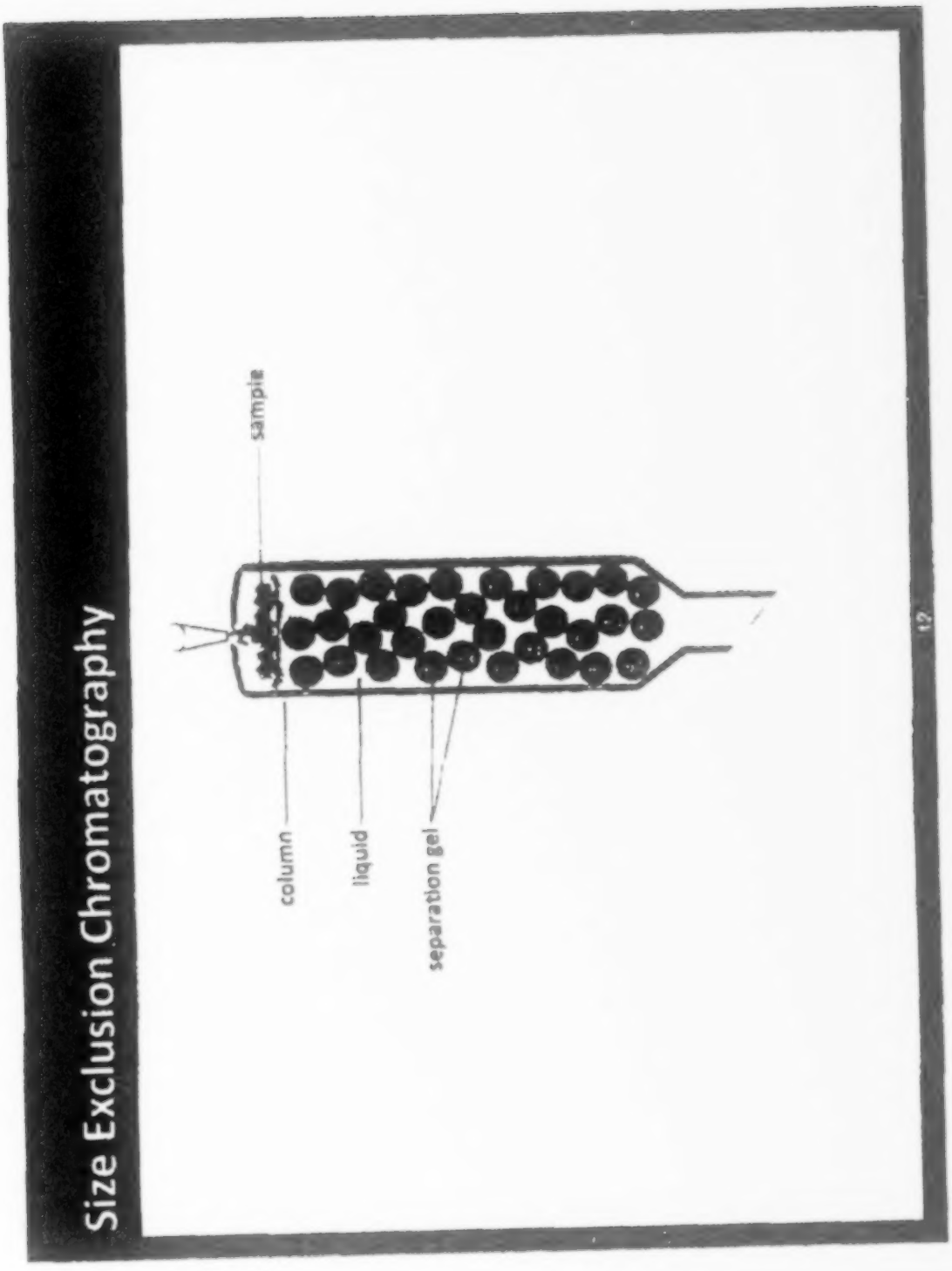
8

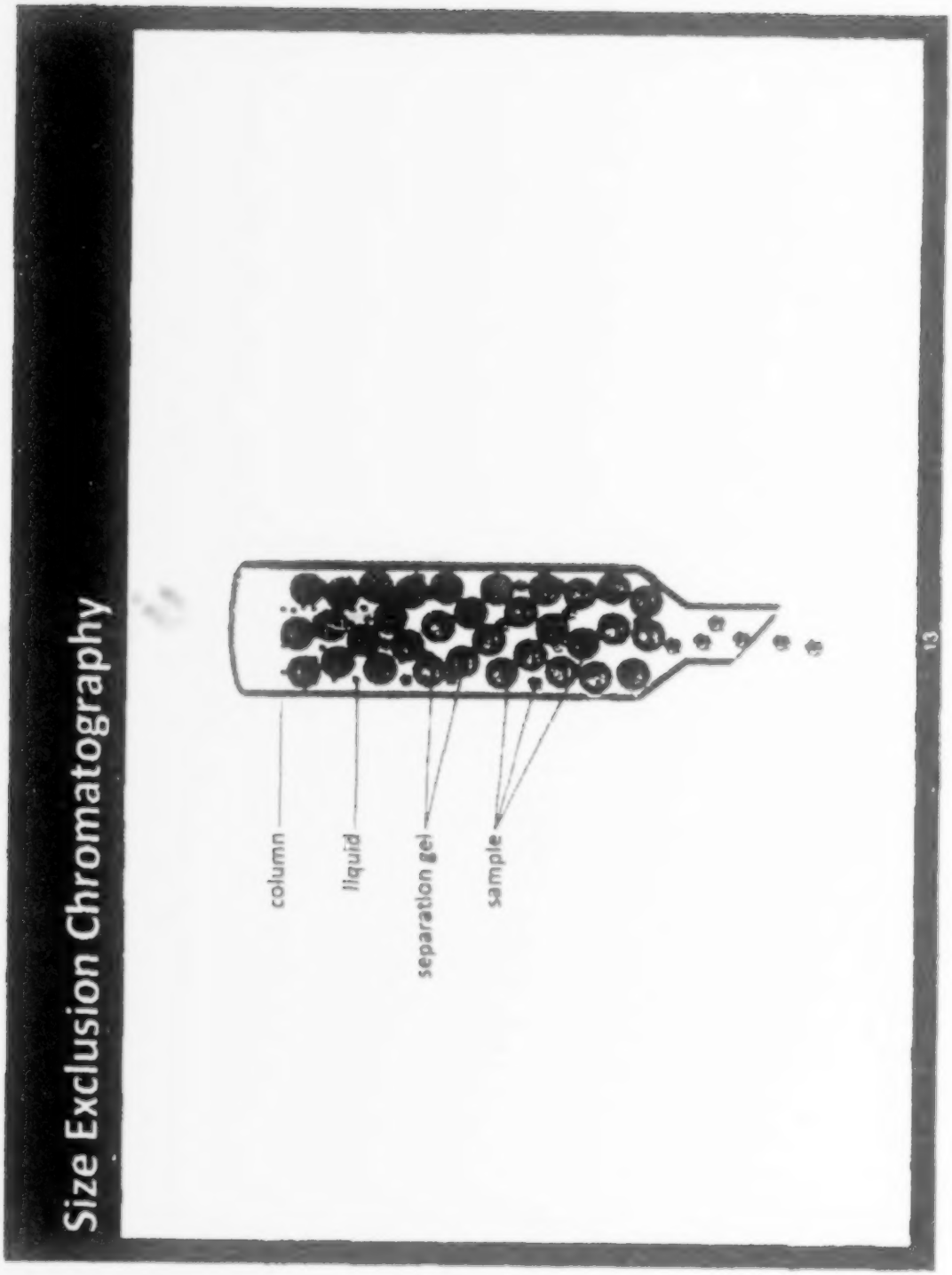
Initial Reaction to Form Copolymer-1

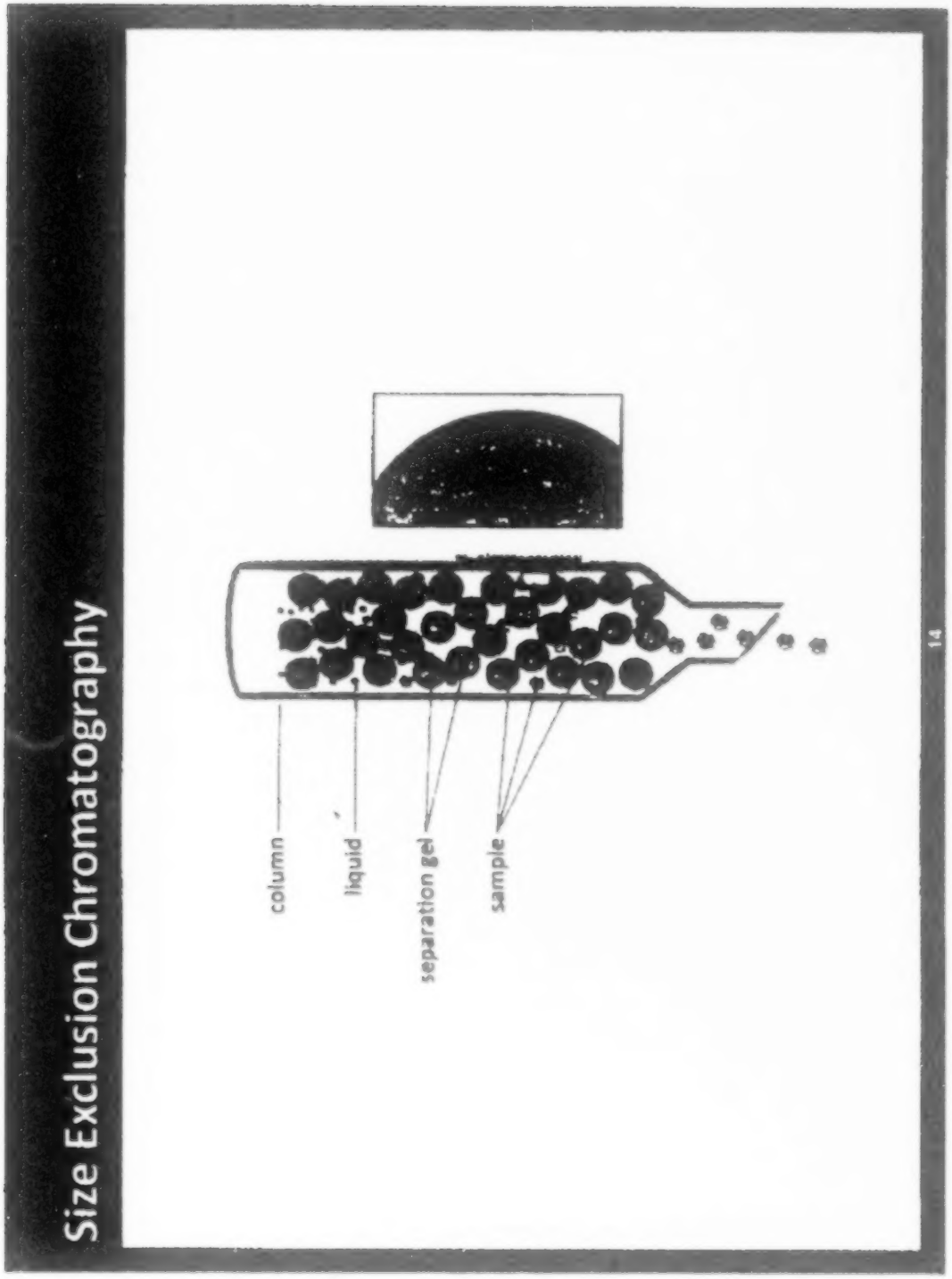
Size Exclusion Chromatography

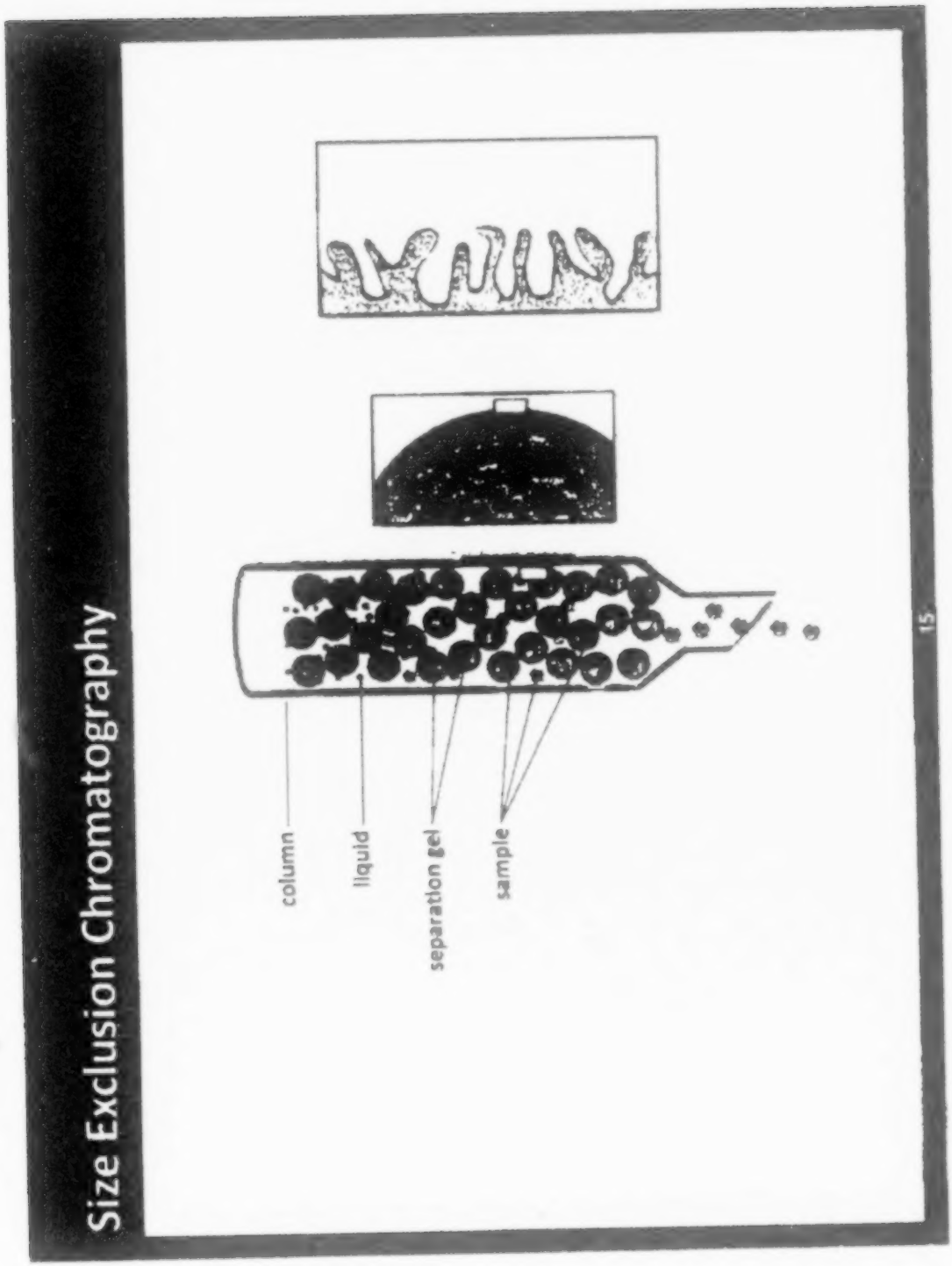


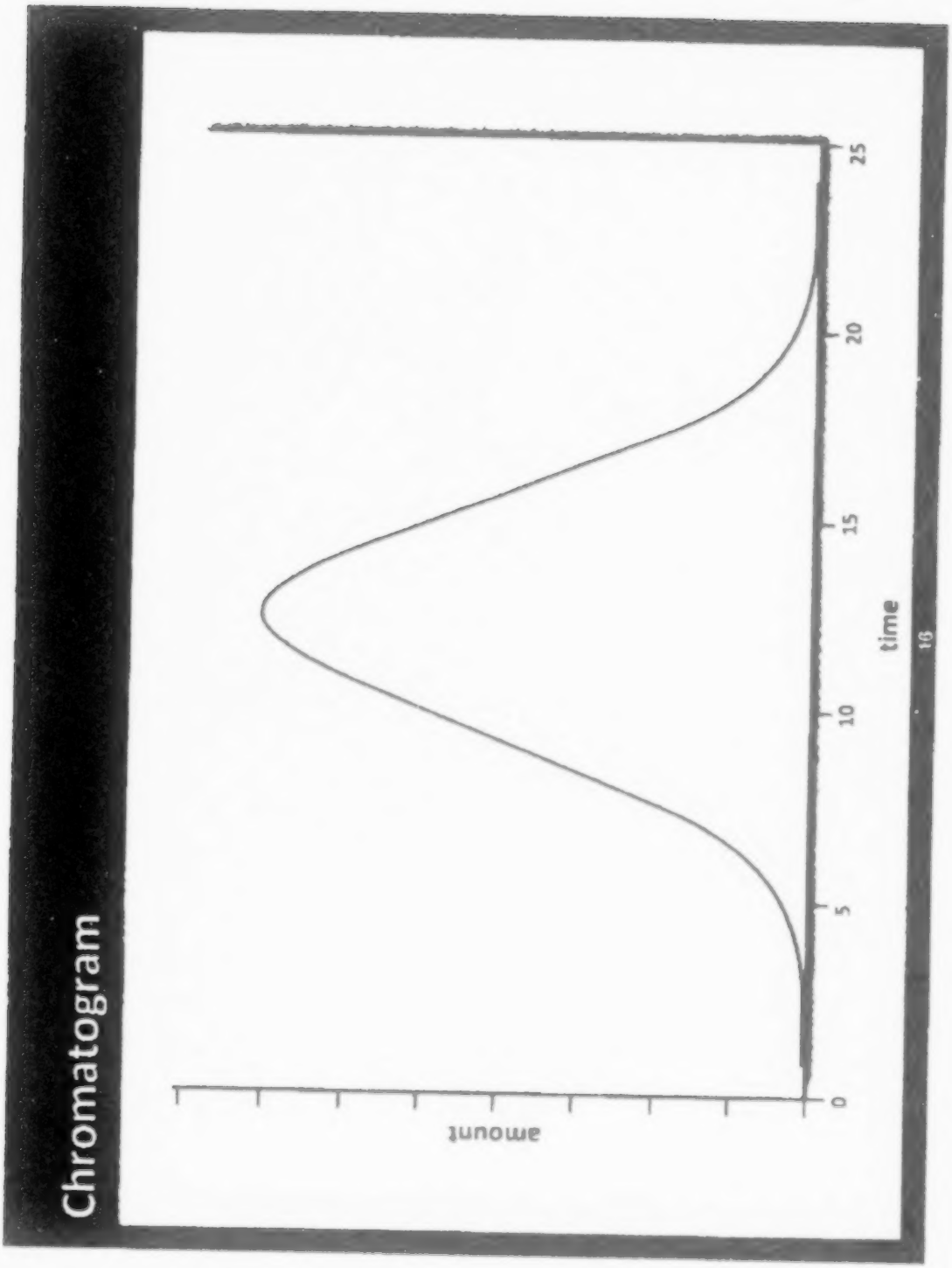

Size Exclusion Chromatography
column
liquid
separation gel

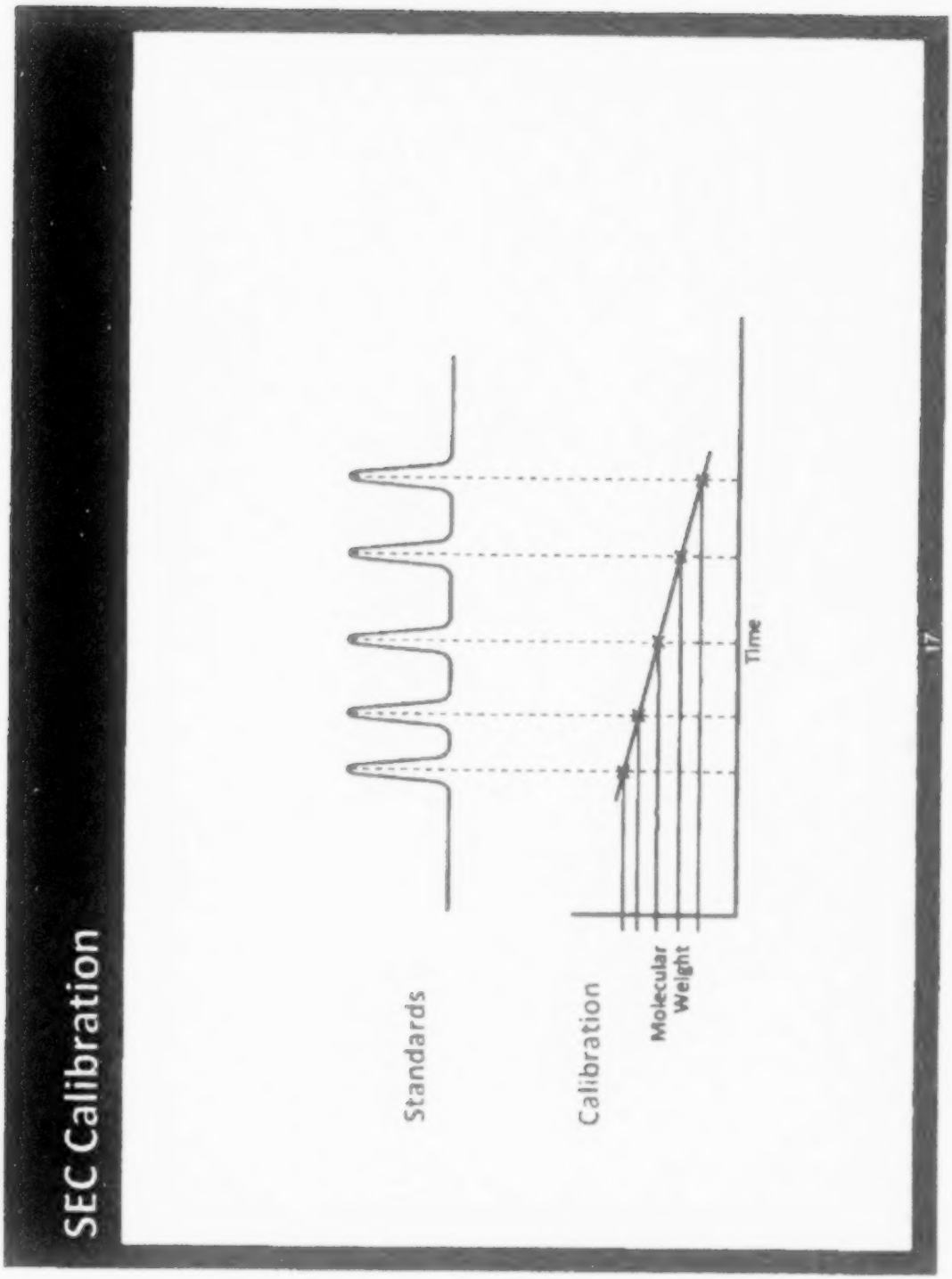

Size Exclusion Chromatography
sample
column
liquid
separation gel

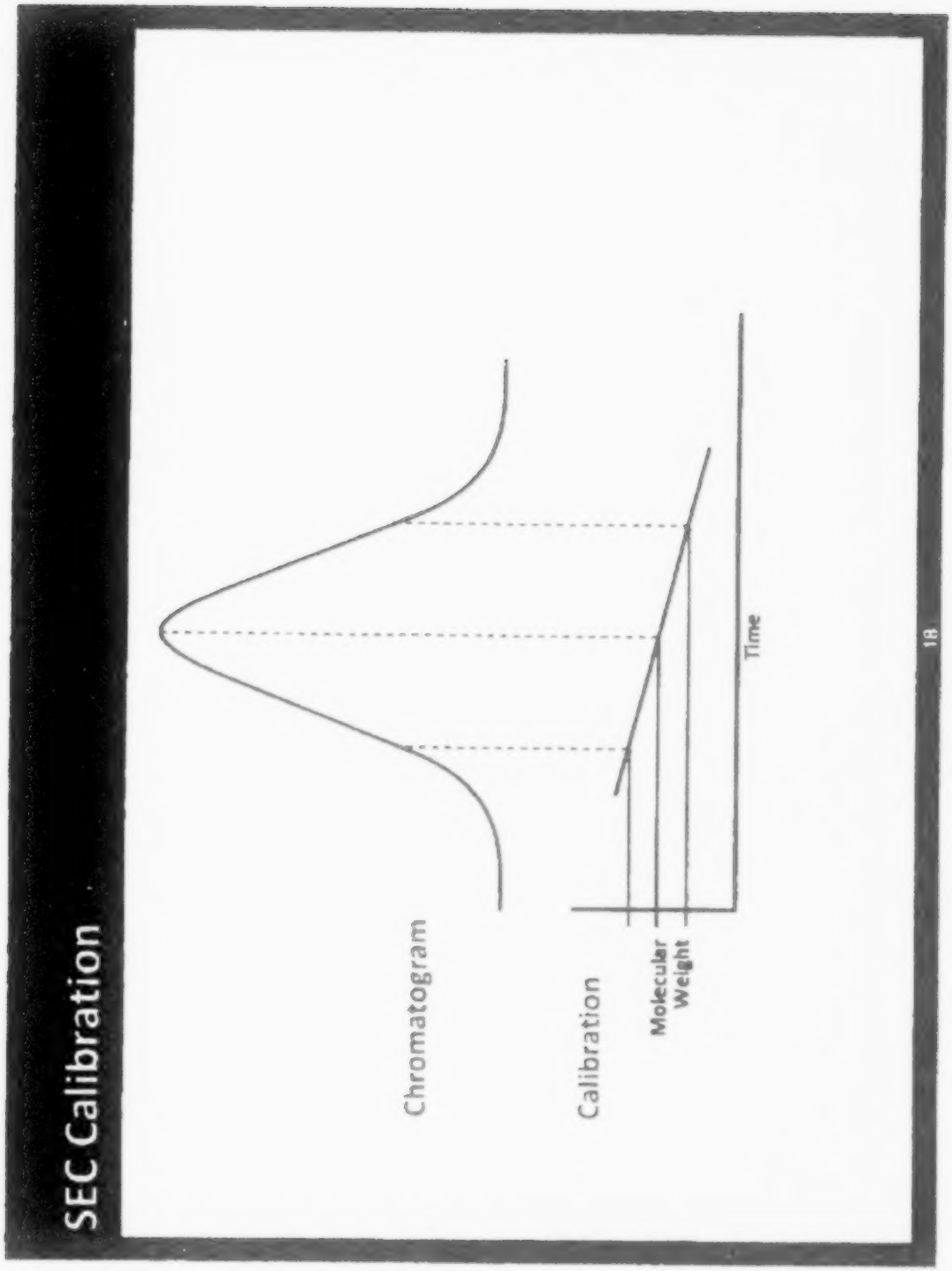

Size Exclusion Chromatography
column
liquid
separation gel
sample
13


Size Exclusion Chromatography
column
liquid
separation gel
sample
14


Size Exclusion Chromatography
column
liquid
separation gel
sample
15


Chromatogram
amount
0
5
10
15
20
25
time


SEC Calibration
Standards
Calibration
Molecular Weight
Time
17

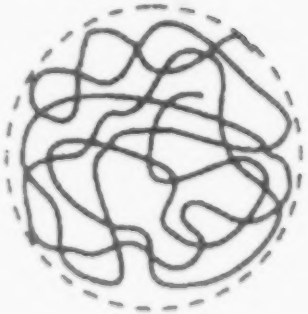

SEC Calibration
Chromatogram
Calibration
Molecular Weight
Time
18

Size/Molecular Weight Relationship

Loosely Coiled Polypeptide
(small size)

Exits the column
later

Loosely Coiled Polypeptide
(large size)



Exits the column
earlier

Size/Molecular Weight Relationship

Loosely Coiled Polypeptide
(small size)

Tightly Coiled Standard
(small size)

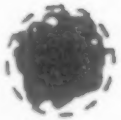
Loosely Coiled Polypeptide
(large size)

- **Same** size as tightly colied standard
- Exits the column at the **same time**, but
- **Lower** molecular weight

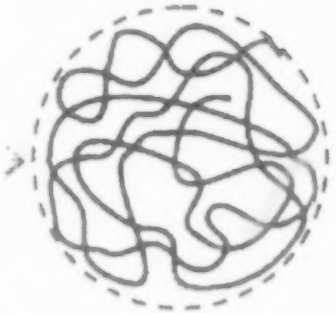
Size/Molecular Weight Relationship

Loosely Coiled Polypeptide
(small size)

Tightly Coiled Standard
(small size)



Loosely Coiled Polypeptide
(large size)



- **Larger** size than tightly coiled standard
- Exits the column **earlier**, but
- **Same** molecular weight

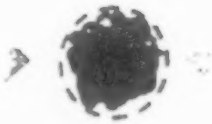
21

Size/Molecular Weight Relationship

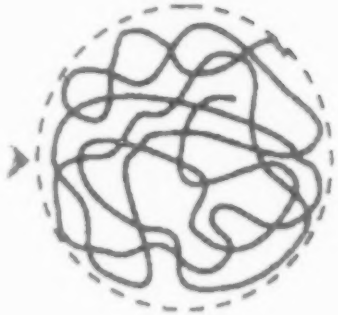
Loosely Coiled Polypeptide
(small size)

- **Same** size as tightly coiled standard
- Exits the column at the **same time**, but
- **Lower** molecular weight

Tightly Coiled Standard
(small size)



Loosely Coiled Polypeptide
(large size)



- **Larger** size than tightly coiled standard
- Exits the column **earlier**, but
- **Same** molecular weight

22

Categories of Molecular Weight Limitations

The molecular weight limitations can be categorized as:

- Average molecular weight
- Copolymer-1 molar fraction
- TFA-Copolymer-1 molar fraction

23

Average Molecular Weight Limitations

"Average molecular weight" limitations appear in claims:

"about 5 to 9 kilodaltons"

'808 patent (claim 1)

'589 patent (claim 1)

"about 4 to about 9 kilodaltons"

'847 patent (claims 1 and 6)

'539 patent (claims 1, 8, 9, 12, 23, 30, and 31)

"6.25 to 8.4 kilodaltons"

'539 patent (claim 10)

Average Molecular Weight - Construction

"peak molecular weight detected using an appropriately calibrated suitable gel filtration column"

Teva v. Sandoz, Mylan Claim Construction Decision, p. 40

Mp Values for Sandoz's Drug Product and Drug Substance

Lot	Peak Average Molecular Weight (Da)
077K7277	8407
037K7253	7275
058K7278	7216
078K7276	7104
129K7276	5932
029K7279	7641
049K7275	6977
019K7276	7366
059K7275	7199
CT0743	8274
CT0750	7417

Source: PTX 351 at SDZ00018608-11;
PTX 349 at SDZ00017949

Sandoz's Product Meets Average Molecular Weight Limitations

Lot	Peak Average Molecular Weight (Da)	"about 5 to 9 kilodaltons"	"about 4 to about 9 kilodaltons"	"6.25 to 8.4 kilodaltons"
[redacted]	8407	✓	✓	✓
[redacted]	7275	✓	✓	✓
[redacted]	7216	✓	✓	✓
[redacted]	7104	✓	✓	✓
[redacted]	5932	✓	✓	
[redacted]	7641	✓	✓	✓
[redacted]	6977	✓	✓	✓
[redacted]	7366	✓	✓	✓
[redacted]	7199	✓	✓	✓
[redacted]	8274	✓	✓	✓
[redacted]	7417	✓	✓	✓

Source: PTX 351 at SDZ00018608-11; PTX 349 at SDZ00017949

Categories of Molecular Weight Limitations

The molecular weight limitations can be categorized as:

- Average molecular weight
- Copolymer-1 molar fraction
- TFA-Copolymer-1 molar fraction

Copolymer-1 Molar Fraction Limitations

"Molar fraction" limitations appear in claims:

Over 75% between 2 – 20 kDa

'430 patent (claims 1–3)

Less than 2.5%...above 40 kDa

'539 patent (claims 8 and 30)

Over 75% between 2 – 20 kDa and less than 2.5%...over 40kDa

'539 patent (claims 9, 10 and 31)

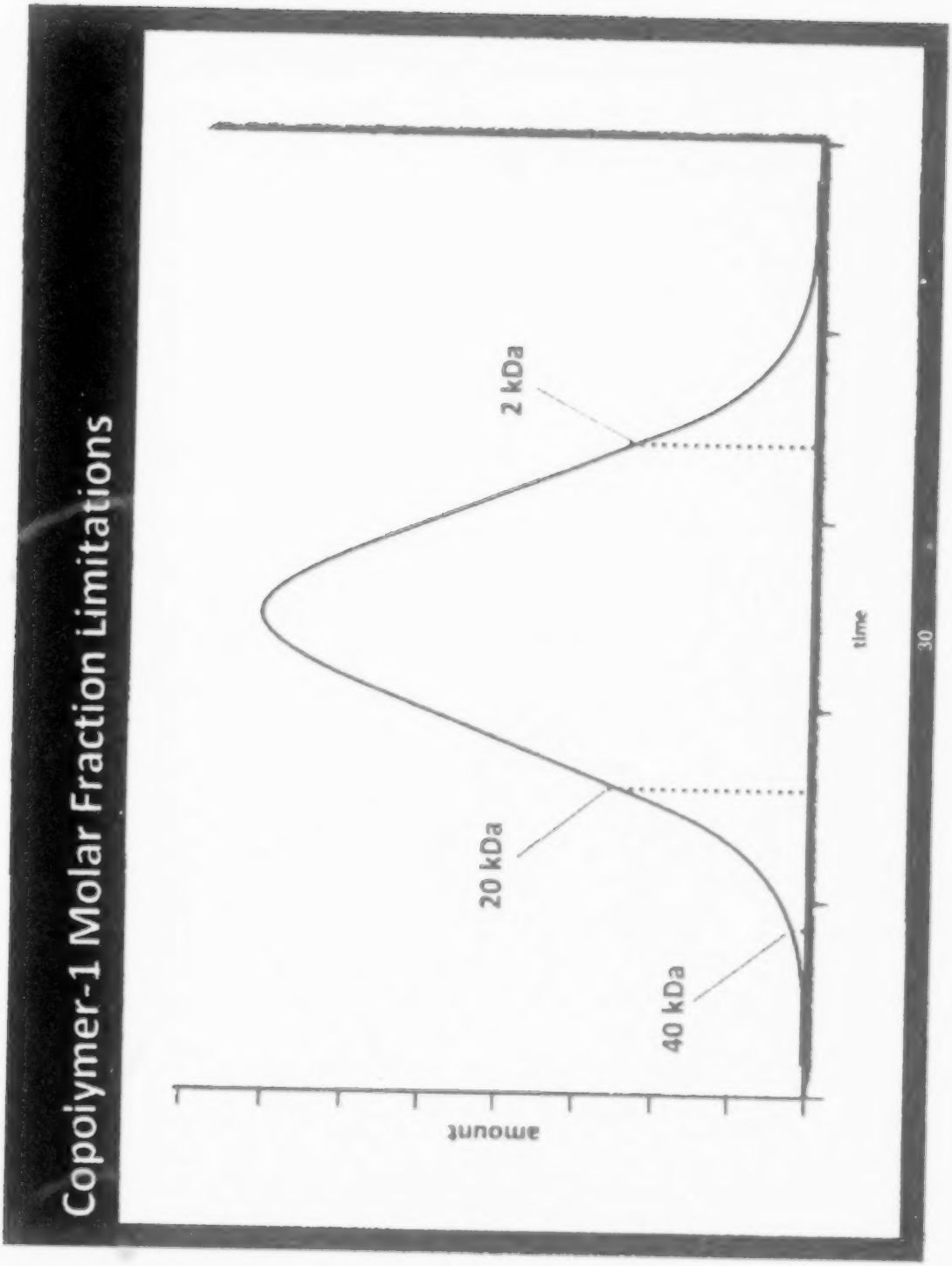
'098 patent (claim 8)

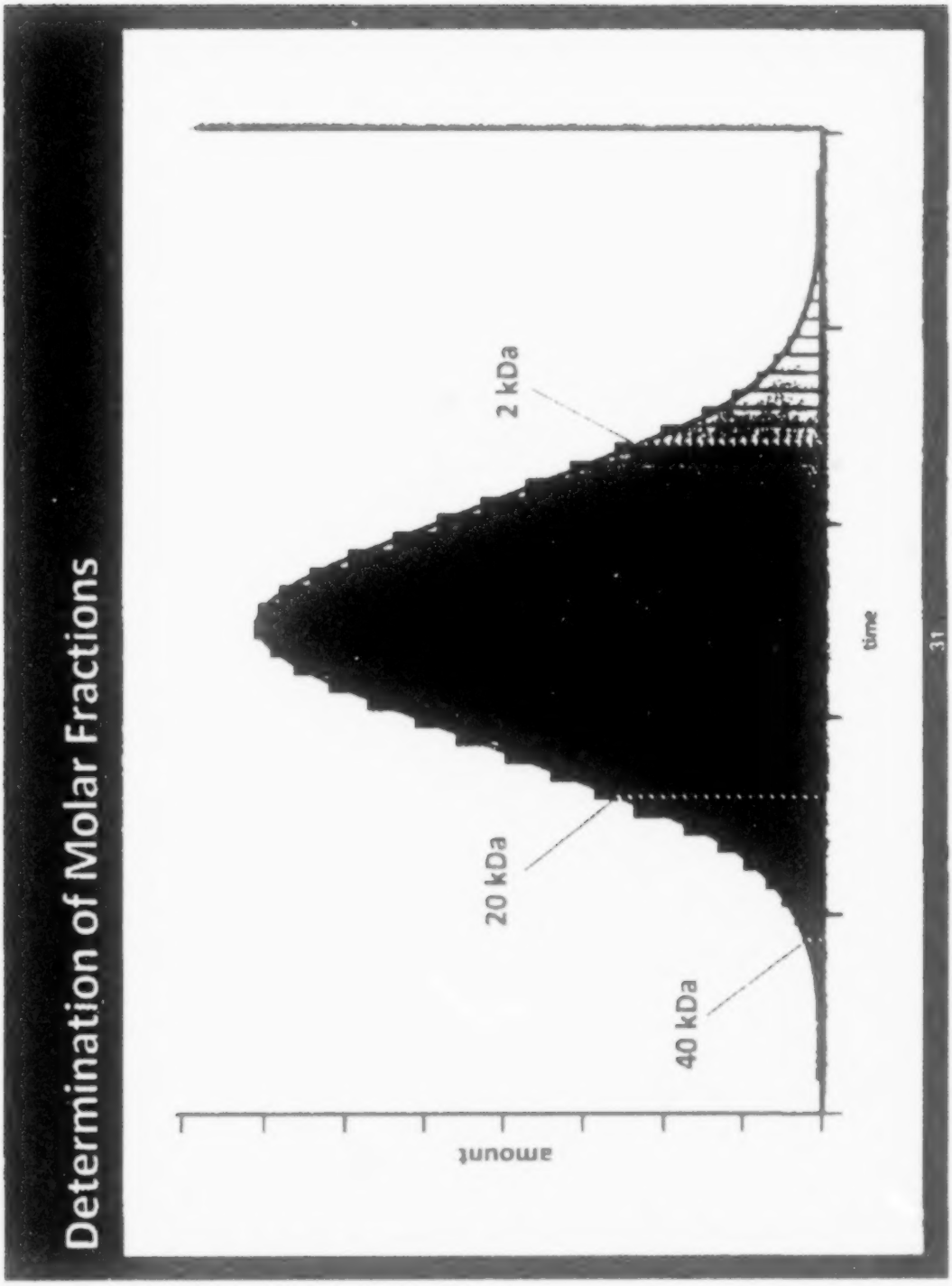
Over 75% between 2 – 20 kDa and less than 5% over 40 kDa

'476 patent (claim 1)

'161 patent (claim 1)

'098 patent (claim 1)


Copolymer-1 Molar Fraction Limitations
amount
time
40 kDa
20 kDa
2 kDa
30


Determination of Molar Fractions
amount
time
2 kDa
20 kDa
40 kDa
31

Calculation of Molar Fraction Percentages

$$\frac{\text{Number of Molecules between 2kDa and 20kDa}}{\text{Total Number of Molecules}} \times 100 = \text{\% Molar Fraction between 2kDa and 20kDa}$$

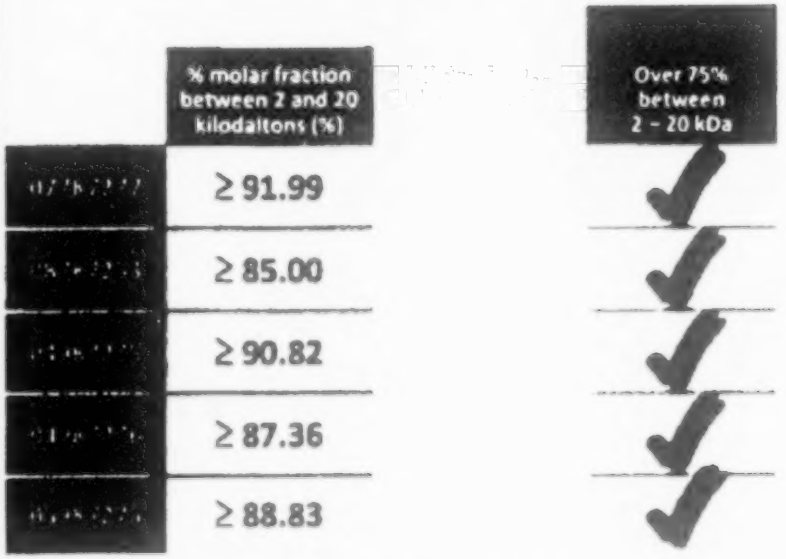
$$\frac{\text{Number of Molecules} > 40\text{kDa}}{\text{Total Number of Molecules}} \times 100 = \text{\% Molar Fraction above 40kDa}$$

Copolymer-1 Molar Fraction Values - Sandoz

	% molar fraction between 2 and 20 kilodaltons (%)	% molar fraction above 40 kilodaltons (%)
077K7277	≥ 91.99	≤ 0.36
087K7253	≥ 85.00	≤ 0.28
049K7275	≥ 90.82	≤ 0.23
049K7276	≥ 87.36	≤ 0.24
059K7275	≥ 88.83	≤ 0.25

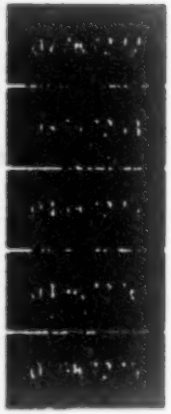
Source: PTX 377

Sandoz's Product Meets Copolymer-1 Molar Fraction Limitations



Source: PTX 377

Sandoz's Product Meets Copolymer-1 Molar Fraction Limitations



% molar fraction above 40 kilodaltons (%)	Less than 2.5%... above 40 kDa
≤ 0.36	✓
≤ 0.28	✓
≤ 0.23	✓
≤ 0.24	✓
≤ 0.25	✓

Source: PTX 377

Sandoz's Product Meets Copolymer-1 Molar Fraction Limitations

	% molar fraction between 2 and 20 kilodaltons (%)	% molar fraction above 40 kilodaltons (%)	Over 75% between 2 – 20 kDa	less than 2.5%... above 40 kDa	Over 75% between 2 – 20 kDa and less than 2.5% over 40 kDa	Over 75% between 2 – 20 kDa and less than 5% over 40 kDa
[redacted]	≥ 91.99	≤ 0.36	✓	✓	✓	✓
[redacted]	≥ 85.00	≤ 0.28	✓	✓	✓	✓
[redacted]	≥ 90.82	≤ 0.23	✓	✓	✓	✓
[redacted]	≥ 87.36	≤ 0.24	✓	✓	✓	✓
[redacted]	≥ 88.83	≤ 0.25	✓	✓	✓	✓

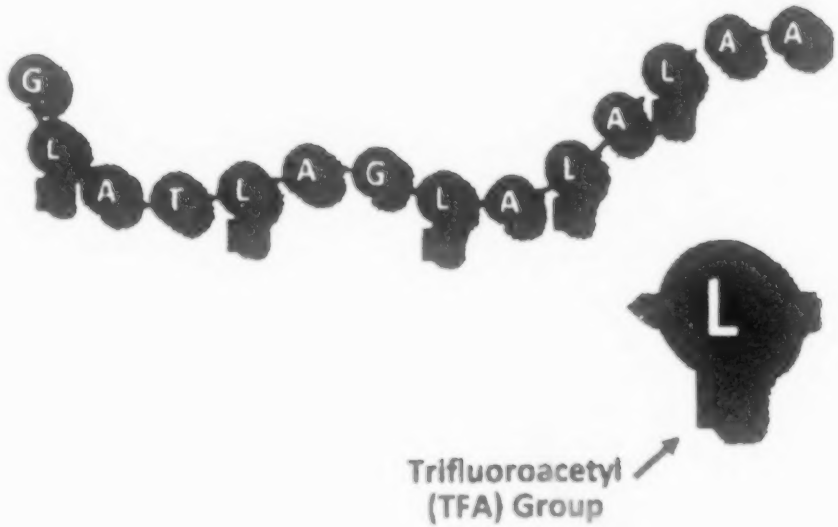
Source: PTX 377

Categories of Molecular Weight Limitations

The molecular weight limitations can be categorized as:

- Average molecular weight
- Copolymer-1 molar fraction
- TFA-Copolymer-1 molar fraction

Trifluoroacetyl (TFA) Copolymer-1



TFA-Copolymer-1 Limitations

"TFA-Copolymer-1" limitations appear in claims:

"trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa"

'430 patent (claims 1–3)

'476 patent (claim 1)

'161 patent (claim 1)

832a

TFA-Copolymer-1 Molar Fraction Values - Sandoz

Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)
[redacted]	≥ 91.45
[redacted]	≥ 89.69
[redacted]	≥ 92.82
[redacted]	≥ 91.34
[redacted]	≥ 92.07

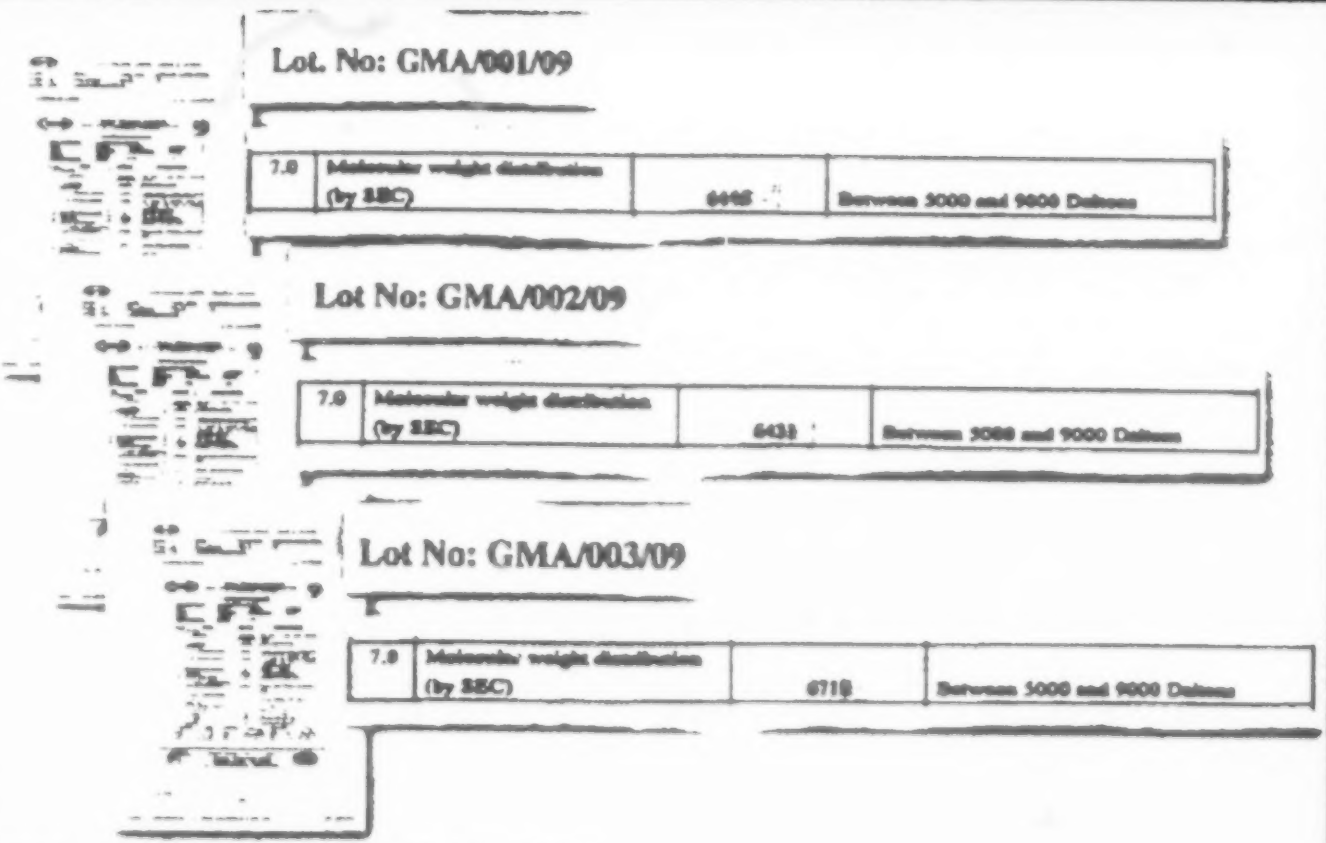
Source: PTX 377

Sandoz's Product Meets TFA-Copolymer-1 Limitations

Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)	"trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa"
077K7277	≥ 91.45	✓
087K7253	≥ 89.69	✓
049K7275	≥ 92.82	✓
049K7276	≥ 91.34	✓
059K7275	≥ 92.07	✓

Source: PTX 377

Mp Values for Mylan's Drug Substance



Lot. No: GMA/001/09

7.0	Molecular weight distribution (by SEC)	6495	Between 5000 and 9000 Daltons

Lot No: GMA/002/09

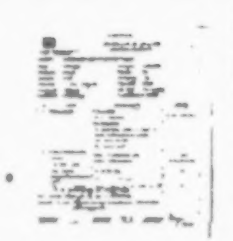
7.0	Molecular weight distribution (by SEC)	6431	Between 5000 and 9000 Daltons

Lot No: GMA/003/09

7.0	Molecular weight distribution (by SEC)	6718	Between 5000 and 9000 Daltons

Source: PTX 325 at: MYL0001050, MYL0001068, MYL0001079

Mp Values for Mylan's Drug Product



BATCH No. : WV901

12.	Molecular Weight distribution by SEC	Between 5000 and 9000 Daltons	[illegible]
	The test will be performed by Analytical division of M/s. Natco Pharma Ltd., and review and report the results from their Certificate of Analysis		

BATCH No. : WV902

12.	Molecular Weight distribution by SEC	Between 5000 and 9000 Daltons	6530
	The test will be performed by Analytical division of M/s. Natco Pharma Ltd., and review and report the results from their Certificate of Analysis		

BATCH No. : WV903

12.	Molecular Weight distribution by SEC	Between 5000 and 9000 Daltons	6086
	The test will be performed by Analytical division of M/s. Natco Pharma Ltd., and review and report the results from their Certificate of Analysis		

Source: PTX 300, 312, 313

Mp Values for Mylan's Drug Product and Drug Substance

Drug Substance

Lot	Peak Average Molecular Weight (Da)
[redacted]	6445
[redacted]	6431
GMA/003/09	6718

Drug Product

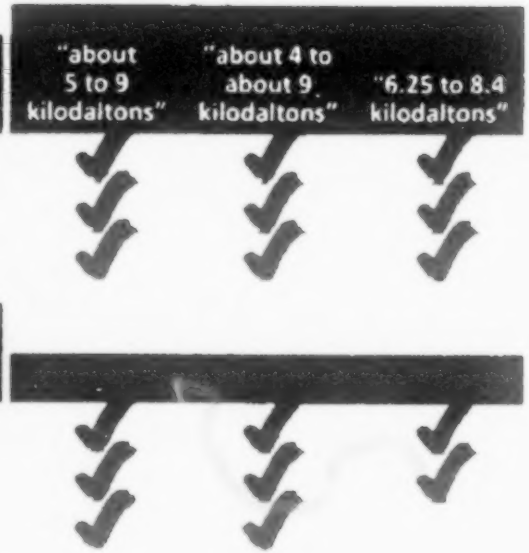
Batch	Peak Average Molecular Weight (Da)
[redacted]	6280
[redacted]	6358
[redacted]	6036

Source: PTX 300, 312, 313, 325

Mylan's Product Meets Average Molecular Weight Limitations

Lot	Peak Average Molecular Weight (Da)
[redacted]	6445
[redacted]	6431
[redacted]	6718

Batch	Peak Average Molecular Weight (Da)
[redacted]	6280
[redacted]	6358
[redacted]	6036



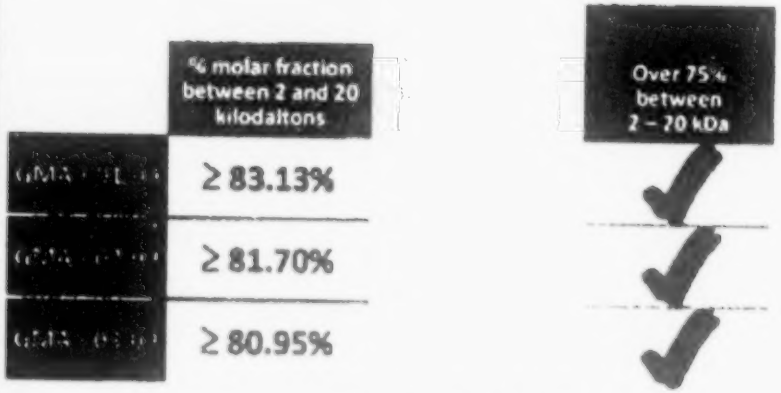
Source: PTX 300, 312, 313, 325

Copolymer-1 Molar Fraction Values - Mylan

	% molar fraction between 2 and 20 kilodaltons (%)	% molar fraction above 40 kilodaltons (%)
GMA 001-09	≥ 83.13%	≤ 0.03%
GMA 002-09	≥ 81.70%	≤ 0.05%
GMA 003-09	≥ 80.95%	≤ 0.04%

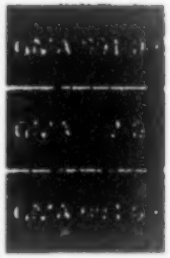
Source: PTX 421

Mylan's Product Meets Copolymer-1 Molar Fraction Limitations



Source: PTX 421

Mylan's Product Meets Copolymer-1 Molar Fraction Limitations



% molar fraction above 40 kilodaltons	Less than 2.5%... above 40 kDa
≤ 0.03%	✓
≤ 0.05%	✓
≤ 0.04%	✓

Source: PTX 421

Mylan's Product Meets Copolymer-1 Molar Fraction Limitations

	% molar fraction between 2 and 20 kilodaltons	% molar fraction above 40 kilodaltons	Over 75% between 2 – 20 kDa	Less than 2.5% above 40 kDa	Over 75% between 2 – 20 kDa and less than 2.5% over 40 kDa	Over 75% between 2 – 20 kDa and less than 5% over 40 kDa
[illegible]	≥ 83.13%	≤ 0.03%	✓	✓	✓	✓
[illegible]	≥ 81.70%	≤ 0.05%	✓	✓	✓	✓
[illegible]	≥ 80.95%	≤ 0.04%	✓	✓	✓	✓

Source: PTX 421

TFA-Copolymer-1 Molar Fraction Values - Mylan

Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)
GMA 001 09	≥ 87.45
GMA 002 09	≥ 86.09
GMA 003 09	≥ 84.52

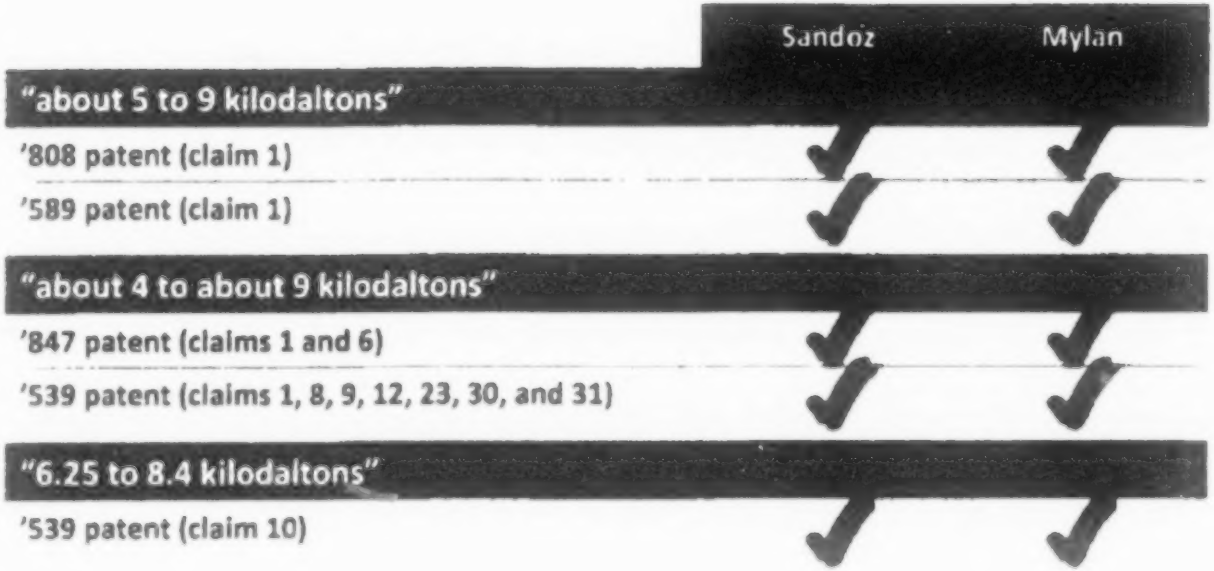
Source: PTX 421

Mylan's Product Meets TFA-Copolymer-1 Limitations

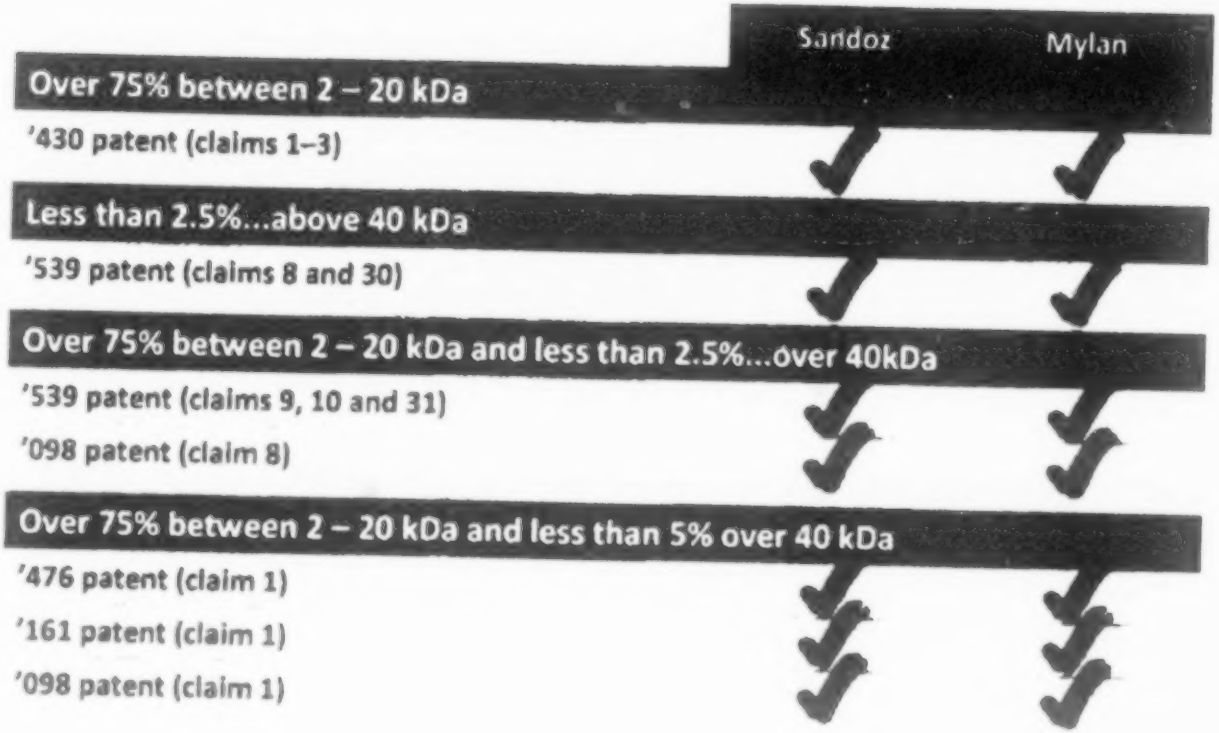
Trifluoroacetyl copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons (%)	"trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa"
GMA-001-09-1176	≥ 87.45	✓
GMA-002-09-1194	≥ 86.09	✓
GMA-003-09-1101	≥ 84.52	✓

Source: PTX 421

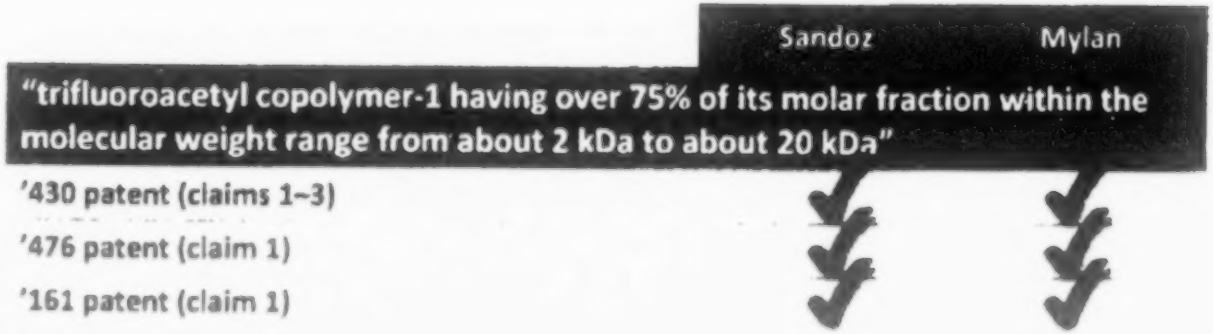
Sandoz and Mylan Meet Average Molecular Weight Limitations



Sandoz and Mylan Meet Copolymer-1 Molar Fraction Limitations



Sandoz and Mylan Meet TFA-Copolymer-1 Limitations



No. 13-854

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

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June 13, 2014

PETITION FOR A WRIT OF CERTIORARI FILED JANUARY 16, 2014
CERTIORARI GRANTED MARCH 31, 2014

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., et al.,	
Plaintiffs,	
v.	08 Civ. 7611 (BSJ) (AJP)
SANDOZ INC., et al.,	
Defendants.	
TEVA PHARMACEUTICALS USA, INC., et al.,	
Plaintiffs,	
v.	09 Civ. 8824 (BSJ) (AJP)
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Defendants.	

BARBARA S. JONES
UNITED STATES DISTRICT JUDGE

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INTRODUCTION

This case involves the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. §§ 355, 360cc (2003); 35 U.S.C. §§ 156 (2002), 271 (2003)) (the "Hatch-Waxman Act"). Plaintiff Teva Pharmaceuticals USA, Inc. holds a patent on a glatiramer acetate product which it markets as Copaxone®, a medicine for treating multiple sclerosis ("MS"). The Defendants have filed abbreviated new drug applications ("ANDAs") with the FDA seeking to market a generic alterative to Copaxone® prior to the expiration of Teva's patents.

The Plaintiffs, Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. (collectively, "Teva") allege infringement. The Defendants, Sandoz Inc., Sandoz International GmbH, Novartis AG, and Momenta Pharmaceuticals, Inc. ("Momenta") (collectively, the "Sandoz" Defendants),[1] Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (collectively, the "Mylan" Defendants[2]) (collectively, with the Sandoz Defendants,

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[1] Teva voluntarily dismissed, without prejudice, their claims against Sandoz International GmbH and Novartis AG. (Dkt. 180 in 08 Civ. 7611(BSJ)(AJP).) Unless noted otherwise, all references to "Sandoz" are to the two remaining Sandoz Defendants—Sandoz Inc. and Momenta Pharmaceuticals, Inc.

[2] Unless noted otherwise, all references to "Mylan" are to all of the Defendants in 09 Civ. 8824.

"Defendants") claim Teva's patents are invalid and unenforceable, among other defenses.

Specifically, Teva filed separate suits, first against the Sandoz Defendants, and second against the Mylan Defendants. The Court consolidated the cases on October 22, 2010. (Dkt. 200 in 08 Civ. 7611.)

Teva alleges Sandoz infringes four U.S. patents— No. 7,199,098, No. 6,939,539, No. 6,054,430, and No. 6,620,847— under 35 U.S.C. §§ 271(a), 271(b), 271(c), and 271 (e) (2). Sandoz counterclaims and seeks a declaratory judgment of non-infringement, unenforceability, and invalidity of nine U.S. patents: No. 7,199,098, No. 6,939,539, No. 6,054,430, No. 6,620,847, No. 5,981,589, No. 6,342,476, No. 6,362,161, No. 5,800,808, and No. 6,048,898. With respect to Mylan, Teva alleges Mylan infringes seven U.S. patents under 35 U.S.C. § 271(e)(2): No. 7,199,098, No. 6,939,539, No. 6,054,430, No. 6,620,847, No. 5,981,589, No. 6,342,476, and No. 6,362,161. Mylan, in turn, counterclaims and seeks a declaratory judgment of non-infringement, unenforceability, and invalidity of the same nine U.S. patents as Sandoz.[3]

I. The Parties

A. Teva

Teva Pharmaceuticals USA, Inc. ("Teva USA") is a Delaware corporation with its principal place of business in North Wales, Pennsylvania. (Joint

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[3] The Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202. Venue is proper pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

Pretrial Order Stipulations ("JPO")¶55.) Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") is an Israeli company with its principal place of business in Israel. (JPO ¶ 56.) Teva Neuroscience, Inc. is a Delaware corporation with its principal place of business in Kansas City, Missouri. (JPO ¶ 57.) Yeda Research and Development Co. Ltd. markets and commercializes new developments from the laboratories of the Weizmann Institute of Science ("Weizmann"). (JPO ¶ 58.) Its principal place of business is in Israel. (JPO ¶ 58.)

B. Sandoz

Sandoz Inc. is a Colorado corporation with its principal place of business in Princeton, New Jersey. (JPO ¶ 62.) Sandoz Inc. does business in the State of New York, including in the Southern District of New York. (First Am. Compl.[4]¶ 6.) Momenta is a Delaware corporation with its principal place of business in Cambridge, Massachusetts. (JPO ¶ 9.) Momenta does business in the State of New York, including in the Southern District of New York. (First Am. Compl. ¶ 9.)

C. Mylan

Mylan Pharmaceuticals Inc. is a West Virginia corporation with its principal place of business in Morgantown, West Virginia. (JPO ¶ 59.) Mylan

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[4] Unless noted otherwise, all references to the First Amended Complaint are to the First Amended Complaint in Teva v. Sandoz, No. 08 Civ. 7611(BSJ)(AJP), and all references to the Complaint are to the Complaint in Teva v. Mylan, No. 09 Civ. 8824(BSJ)(AJP).

Pharmaceuticals does business in the State of New York, including in the Southern District of New York. (Mylan Answer ¶ 8.) Mylan Inc. is a Pennsylvania corporation with its principal place of business in Canonsburg, Pennsylvania. (JPO ¶ 60.) Mylan Inc. does business in the State of New York, including in the Southern District of New York. (Mylan Answer ¶ 9.) Natco Pharma Ltd. ("Natco") is an Indian company with its principal place of business in India. (JPO ¶ 61.) Natco does business in the State of New York, including in the Southern District of New York. (Natco Answer ¶ 10.)

II. The Patents-in-Suit

A. Overview

The patents-in-suit are U.S. Patent Nos. 5,981,589 ("'589 Patent"), 6,054,430 ("'430 Patent"), 6,342,476 ("'476 Patent"), 6,362,161 ("'161 Patent"), 6,620,847 ("'1847 Patent"), 6,939,539 ("'539 Patent") and 7,199,098 ("'098 Patent") (collectively, the "Orange Book Patents") and U.S. Patent Nos. 5,800,808 ("'808 Patent") and 6,048,898 ("'898 Patent") (collectively with the Orange Book Patents, the "patents-in-suit"). (JPO ¶ 64.) Each of the patents-in-suit is entitled "Copolymer-1 improvements in compositions of copolymers." (JPO ¶ 67.) The four inventors named on the patents-in-suit are Eliezer Konfino, Michael Sela, Ruth Arnon, and Dvora Teitelbaum. (Plaintiffs' Trial Exhibits ("PTX") 1-9.) Eliezer Konfino worked for Teva and retired from the company in December

1991.[5] Michael Sela, Ruth Arnon, and Dvora Teitelbaum worked at Weizmann. (JPO ¶ 66.)

The patents-in-suit each claim priority to (i) U.S. Patent Application No. 08/248,037, filed May 24, 1994 ("'037 application"), abandoned, and (ii) Patent Application No. 08/344,248, filed November 23, 1994 ("'248 application"), also abandoned. (JPO ¶¶ 79-80.) The substantive portion of the patent specification is identical for each of the patents-in-suit. Accordingly, for ease of reference, unless noted otherwise, all citations to the specification are to the '808 patent specification.

The patents-in-suit are directed to improved compositions of copolymer-1. (PTX 1 at 1:1-2.) The patents explain that the improved compositions consist of a lower molecular weight form of copolymer-1 that may be used for the treatment of multiple sclerosis. (PTX 1 at 1: 43-53.)

The patent specification defines the molecular weight characteristics of the lower molecular weight copolymer-1 in several ways. The patent specification explains, for example, that the lower molecular weight copolymer-1 can be substantially free of species over 40 kilodaltons ("kDa"), and it describes a preferred composition that has "less than 5% of species" having a molecular weight over 40 kDa. The patents also describe a more preferred composition having "less than 2.5% of species"

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[5] The Stipulations do not specify for which Teva entity Konfino worked.

having a molecular weight over 40 kDa. (PTX 1 at 1:64-2:4.)

In addition, the patents describe the claimed lower molecular weight copolymer-1 as "having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa." (PTX 1 at 2:5-7.) A "molar fraction" in this context refers to the proportion of molecules (as measured by the number of "moles" of molecules) between 2 kDa and 20 kDa, as compared to the total number (or "moles") of all of the molecules in the sample.

Finally, the lower molecular weight copolymer-1 is defined in the patents-in-suit by its average molecular weight. The patent specification provides various ranges for the average molecular weight values for the lower molecular weight copolymer-1. Those ranges are reflected in the asserted claims, which are discussed in further detail below. The patents also describe a synthetic process for making the claimed copolymer-1. (PTX 1 at 4:28-6:3.)

The patent specification describes two ways of producing a lower molecular weight copolymer-1. (PTX 1 at 2:14-41, 2:51-3:18, 4:28-6:3.) First, in Example 1, the patents describe making copolymer-1 and then "fractionating"—or dividing into smaller portions—the resulting copolymer-1 to isolate a low molecular weight fraction. (PTX 1 at 2:57-3:2.) In addition, the patents provide examples describing processes for making copolymer-1 of varying molecular weights. (PTX 1 at 4:28-6:3.) Second, the patents describe the use of a particular reagent in the synthetic process—hydrobromic acid in the form

of hydrogen bromide ("HBr") in acetic acid—to cleave an intermediate product called protected copolymer-1 polypeptides into smaller polypeptides. The patents-in-suit teach that the time and temperature of the HBr/acetic acid treatment step can be varied to control the amount of cleavage that occurs, and hence, the molecular weight of the resulting copolymer-1. (PTX 1 at 4:59-6:3.)

The patent specification describes the use of a calibrated size exclusion chromatography ("SEC") column, Superose 12, to measure the molecular weight distribution and average molecular weight of copolymer-1 samples. (PTX 1 at 3:6-13.)

Example 2, entitled "Toxicity Analysis," appears in the specification of each of the patents-in-suit and describes two different toxicity tests for copolymer-1: the in vivo mouse test and the in vitro rat basophilic leukemia ("RBL") degranulation test. (PTX 1 at 3:21-4:27.) Referring to the in vivo mouse test, Example 2 states that "[t]hree batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 kDa (less than 2.5% copolymer-1 species over 40 kDa) and 22 kDa (more than 5% copolymer-1 species over 40 kDa) were subjected to the toxicity test" in which five mice in each experimental group were injected with the test solution. (PTX 1 at 3:23-40.) It goes on to state that "[if], at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated 'non-toxic'" and if "one or more of the mice had died or had shown adverse signs, then the batch was designated 'toxic'." (PTX 1 at 3:36-40.) In regard to the in vivo test, Example 2 concludes that "the batches with the average

molecular weight of 7.3 and 8.4 kDa were both designated 'non-toxic', whereas in the batch with the average molecular weight of 22 kDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated 'toxic.'" (PTX 1 at 3:41-45.)

With respect to the RBL degranulation test, Example 2 explains that the purpose of this test was to "screen out those batches of copolymer-1 which invoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (PTX 1 at 3:63-67.) Example 2 reports that "[f]our batches of copolymer-1, with average molecular weight between 6,250-14,500, were analyzed for both % of the species with molecular weight over 40 kDa and for degranulation of RBL's." (PTX 1 at 4:11-15.)

Example 2 sets forth the results of the RBL degranulation test in the following table:

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7300	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

(PTX 1 at 4:15-24.) In regard to the RBL test data, Example 2 concludes, " [a]s can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin indicative of toxicity is low, and vice versa." (PTX 1 at 4:25-27.)

The patent specification also describes pharmaceutical compositions comprising the lower molecular weight copolymer-1, as well as the treatment of multiple sclerosis using lower molecular weight copolymer-1. (PTX 1 at 1:51-53.)

B. Copaxone® - Teva NDA

Teva USA is the holder of New Drug Application ("NDA") No. 20-622, for glatiramer acetate, which was approved by the United States Food and Drug Administration ("FDA") on December 20, 1996. (JPO ¶¶ 82, 83.) The Teva entities market and sell glatiramer acetate under the trade-name Copaxone® in the United States. (JPO ¶ 84.) Glatiramer acetate is a form of copolymer-1. (Sept. Tr. (Grant) 220:13-221:2; Sept. Tr. (Owens) 630:11-631:8; PTX 206 at SDZ00000031; PTX 320 at MYL0000236.) Copaxone® was first offered for sale in the United States on April 2, 1997. (Sept. Tr. (Congleton) 45:14-21.) It is approved for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis ("RRMS"), including patients who have experienced a first clinical episode and have magnetic resonance imaging features consistent with multiple sclerosis. (JPO ¶ 85.)

Each of the patents-in-suit is assigned to and owned by Yeda. (JPO ¶ 68.) Teva Ltd. is the exclusive licensee of each of the patents-in-suit. (JPO ¶ 69.) The Teva entities caused the Orange Book Patents to be listed in the FDA's publication, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book"). (JPO ¶ 65.)

C. Sandoz's and Momenta's ANDA

Momenta entered into a collaboration and license agreement with Sandoz AG on June 13, 2007, regarding, among other things, the development of a generic Copaxone® product. (PTX 957 (Brugger Dep.) at 105:12-106:08; PTX 175.) Sandoz Inc. submitted an ANDA, No. 90-218, on December 27, 2007, seeking approval from the FDA to manufacture and sell a generic Copaxone® product before the expiration of the Orange Book Patents. (JPO ¶¶ 92, 93.)

[redacted] Sandoz Inc. submitted a major amendment to its ANDA. (Sept. Tr. (Grant) 221:8-164; PTX 351.) [redacted], Sandoz Inc. submitted a "Briefing Book" to the FDA, in advance of [redacted] meeting between Sandoz Inc. and the FDA regarding Sandoz's ANDA ("Briefing Book"). (Sept. Tr. (Gokel) 419:19-420:5; PTX 913.) The Briefing Book, among other things, described changes that Sandoz Inc. planned to make to its manufacturing process. (PTX 913.) Sandoz amended its ANDA on [redacted]. (Hagberg Reply Decl. Ex. A.)

Pursuant to 21 U.S.C. § 355 (j) (2) (A) (vii) (IV) , Sandoz Inc. filed a certification with the FDA, alleging that the claims of the Orange Book Patents are invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Sandoz's ANDA proposed glatiramer acetate product ("Paragraph IV Certification"). (JPO ¶ 94.) Sandoz Inc. sent a letter ("the Notice Letter"), dated July 10, 2008, to Teva

USA, Teva Ltd., Teva Neuroscience, and Yeda, notifying them that Sandoz Inc. filed an ANDA for glatiramer acetate and was providing information to Teva pursuant to 21 U.S.C. § 355(j) (2) (B) (i)-(ii). (JPO ¶ 95.)

On August 28, 2 008, Teva sued Sandoz Inc. and Momenta for infringement of the Orange Book Patents. Teva Pharmaceuticals USA, Inc., v. Sandoz Inc., No. 08 Civ. 7611 (BSJ)(AJP) (S.D.N.Y.). (JPO ¶ 97.) Sandoz Inc. and Momenta counterclaimed for, among other things, a declaratory judgment of non-infringement, invalidity, and unenforceability of all nine patents-in-suit. (Dkt. 14 at ¶¶ 89-116 in No. 08 Civ. 7611; Dkt. 16 at ¶¶ 89-116 in No. 08 Civ. 7611.)

D. Mylan and Natco ANDA

Mylan Inc. and Natco signed an agreement, dated June 7, 2008, relating to the development and marketing of a glatiramer acetate product in the United States. (JPO ¶ 87; PTX 245.) On June 29, 2009, Mylan Pharmaceuticals submitted an ANDA, No. 91-646, seeking approval to manufacture and sell Mylan's proposed glatiramer acetate product before the expiration of the Orange Book Patents. (JPO ¶¶ 86, 88.) [redacted] On April 19, 2011, the Mylan entities submitted a major amendment to the ANDA. (DTX 1411.) The major amendment did not make any changes to the manufacturing process.

Pursuant to 21 U.S.C. § 355 (j) (2) (A) (vii) (IV), Mylan Pharmaceuticals filed a certification with the FDA, alleging that the claims of the Orange Book Patents are invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale or offer for sale of Mylan's proposed glatiramer acetate product ("Paragraph IV Certification"). (JPO ¶ 89.) Mylan Pharmaceuticals sent a notice letter, dated September 16, 2009, to Teva USA, Teva Ltd., Teva Neuroscience, and Yeda, notifying them that Mylan filed an ANDA for glatiramer acetate and was providing information to Teva pursuant to 21 U.S.C. § 355 (j) (2) (B) (ii). (JPO ¶ 90.)

On October 16, 2009, Teva and Yeda sued the Mylan entities and Natco for infringement of the Orange Book Patents. Teva Pharmaceuticals USA, Inc., v. Mylan Pharmaceuticals, Inc., No. 09 Civ. 8824(BSJ)(AJP) (S.D.N.Y.). (JPO ¶ 91.) The Mylan Defendants counterclaimed for, among other things, a declaratory judgment of non-infringement and invalidity of all nine patents-in-suit. (Dkt. 8 at ¶¶ 82-117 in 09 Civ. 8824; Dkt. 34 at ¶¶ 187-224 in 09 Civ. 8824.)

III. Procedural History and Claim Construction

Teva and Sandoz submitted claim construction briefing in late 2009, and a claim construction hearing was held on January 20, 2010. (Dkts. 68-72, 76-82, 89-93, 96-97, 102, 104-05, 114-19 in 08 Civ. 7611.) Sandoz moved for summary judgment on the basis of indefiniteness on December 23, 2009. (Dkts. 120-22 in 08 Civ. 7611.) On September 7, 2010, the

Court denied Sandoz's motion for summary judgment. (Dkt. 181 in 08 Civ. 7611.) Sandoz subsequently submitted supplemental claim construction briefing regarding the term "average molecular weight." (Dkts. 192-93, 204-06 in 08 Civ. 7611.)

Teva and Mylan submitted claim construction briefing from April to July 2010. (Dkts. 38-39, 41, 43-45, 57-65 in 09 Civ. 8824.) Mylan moved for summary judgment on the basis of indefiniteness on November 15, 2010. (Dkt. 96-98 in 09 Civ. 8824.) On August 24, 2011, the Court issued a Memorandum and Order denying Mylan's motion for summary judgment and construing the disputed claim terms as follows:

> "Copolymer-1" is construed to mean "a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides." (Claim Construction Order ("CCO") at 12.)
>
> "Average molecular weight" is construed to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Id. at 40.)[6]

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[6] There are different types of average molecular weights, including number average ("Mn"), weight average ("Mw"), z-

"Copolymer-1 having a molecular weight" is construed to mean "copolymer-1 having a peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (Id. at 40, n.10.)

"Polypeptides composed of glutamic acid, lysine, alanine and tyrosine" is construed to mean "more than one polypeptide, each consisting essentially of glutamic acid, lysine, alanine and tyrosine residues." (Id. at 14-15.)

"Copolymers of alanine, glutamic acid, lysine and tyrosine" is construed to mean "more than one polymer molecule, each consisting essentially of glutamic acid, lysine, alanine and tyrosine residues." (Id. at 15.)

"Copolymer-1 fraction" is construed to mean "a portion of a copolymer-1 mixture having a narrower molecular weight distribution than the starting protected copolymer-1 mixture." (Id. at 16.)

"Toxicity" is construed to mean "the degree to which a substance exhibits negative effects in mouse mortality or RBL degranulation test." (Id. at 44.)

"Predetermined" is construed to mean "determined beforehand." (Id. at 47.)

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average ("Mz"), and viscosity average ("Mv"), in addition to "peak average" ("Mp"). (Sept. Tr. 1195:6-19 (Scandella).)

"Predetermined by a test reaction" is construed to mean "determined beforehand by a reaction carried out to determine results of varying reaction conditions." (Id. at 50.)

(Dkt. 273 in 08 Civ. 7611; Dkt. 194 in 09 Civ. 8824.)

A. July 2011 Inequitable Conduct Trial

After denying Teva's motion for a summary judgment finding of no inequitable conduct (Dkt. 232 in 08 Civ. 7611; Dkt. 141 in 09 Civ. 8824), the Court held a bench trial regarding Defendants' inequitable conduct defense in July 2011. The Court heard live testimony from the following witnesses:

i. Teva's Witnesses

Dr. Irit Pinchasi

Dr. Irit Pinchasi is a former Vice President for Innovative R&D at Teva.[7] (July Tr. (Pinchasi) 13:13-17.) Dr. Pinchasi testified regarding the research and development of Teva's Copaxone® product; the inventions described in the patents-in-suit; the technology related to those inventions; and Teva's initial patent application filed in May 1994.

Professor Ruth Arnon

Professor Ruth Arnon is a named inventor on the patents-in-suit. (PTX 1.) She is currently Professor Emeritus at Weizmann and President of the Israel

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[7] At trial, Pinchasi did not specify for which Teva entity she worked.

Academy of Sciences and Humanities. (July Tr. (Arnon) 303:14-17.) She was formerly the Chair of the Department of Chemical Immunology, Dean of the Faculty of Biology, and Vice President of Weizmann. (July Trial Tr. (Arnon) 307:16-21.)

Professor Arnon testified regarding the discovery and development of copolymer-1; the inventions of the patents-in-suit; the technology related to those inventions; and the initial patent application filed in May 1994.

Dr. Barbara Baird

Dr. Barbara Baird is the Horace White Professor and Chair of the Department of Chemistry and Chemical Biology at Cornell University. (July Tr. (Baird) 569:7-11; PTX 768.) Dr. Baird is an expert in the RBL degranulation test, and has been using this test for over thirty years. (July Tr. (Baird) 572:7, 573:6-14, 576:10-12, 585:22-586:1.)

At trial, Dr. Baird testified regarding the RBL degranulation test and its use by Weizmann and Teva, including in the patents-in-suit.

ii. Defendants' Witnesses

Dr. Ian Kimber

Dr. Ian Kimber is Chair of the Department of Toxicology at the University of Manchester. His research has covered immunology and toxicology, with a particular focus on the regulation of immune responses and allergic disease. (July Tr. (Kimber) 368:17-20.) At trial, he testified regarding the

toxicity testing described in the patents-in-suit.
Eugene Rzucidlo

Eugene Rzucidlo is an attorney at the law firm Hershkovitz & Associates who practices before the United States Patent and Trademark Office ("PTO"). He was previously a patent examiner at the PTO and a member of the Board of Patent Appeals. (July Tr. (Rzucidlo) 498:24-499:8.) He has practiced before the PTO continuously since 1985. (July Tr. (Rzucidlo) 499:16-500:11.)

At trial, Rzucidlo testified regarding the process of patent prosecution and the prosecution histories of the patents-in-suit.

B. September 2011 Infringement and Invalidity Trial

Starting on September 7, 2011, the Court held a bench trial regarding Plaintiffs' infringement claims and Defendants' remaining non-infringement and invalidity defenses. The Court heard testimony from Sandoz on its non-infringement, obviousness, lack of enablement, and indefiniteness defenses. The Court heard testimony from Mylan on its non-infringement, best mode, and obviousness defenses. During the trial, Mylan notified Plaintiffs and the Court that it was no longer asserting that the patents are invalid based on anticipation or public use. (Sept. Tr. 1349:9-1351:24.)

At the September trial, the Court heard live testimony from the following witnesses:

i. Teva's Witnesses

Jon Congleton

Jon Congleton is the Senior Vice President and General Manager of Teva Neuroscience. (Sept. Tr. (Congleton) 39:19-22.) He has been with Teva Neuroscience for over fifteen years. (Sept. Tr. (Congleton) 41:12-13.) Prior to becoming Senior Vice President, Congleton served as both product director and director of marketing for Copaxone® (Sept. Tr. (Congleton) 42:1-13.)

At trial, Congleton testified regarding the nature of Teva's business, sales and marketing of Copaxone®, and the history and state of the market for multiple sclerosis treatments.

Dr. Robert Lisak

Dr. Robert Lisak has been the Chairman of the Department of Neurology and Professor of Immunology and Microbiology at Wayne State University for the past twenty-five years. He is also Chief of Neurology at Harper University Hospital. (Sept. Tr. (Lisak) 78:6-79:7, 84:6-11; PTX 419.) He is an expert in multiple sclerosis and its treatment. (Sept. Tr. (Lisak) 87:24-88:6.)

Dr. Lisak testified regarding multiple sclerosis and its treatment; the long-felt need for a drug like Copaxone®; the failure of others to develop safe and effective multiple sclerosis treatments; and Defendants' infringement of claim limitations related to treating multiple sclerosis.

Dr. Gregory Grant

Dr. Gregory Grant is a Professor of Biochemistry in Medicine and Developmental Biology at the School of Medicine at Washington University School of Medicine. (Sept. Tr. (Grant) 178:9-13; PTX 760.) He is also Director of the Protein and Nucleic Acid Chemistry Laboratories of Washington University. (Sept. Tr. (Grant) 178:14-17; PTX 760.) He is an expert in the characterization of proteins and polypeptides using size exclusion chromatography. (Sept. Tr. (Grant) 188:11-17.)

Dr. Grant testified regarding the background of the chemistry and molecular weight measurement technique described in the patents-in-suit and Defendants' infringement with regard to the claim limitations relating to molecular weight. He also provided rebuttal testimony regarding the issues of non-obviousness, definiteness, and enablement.

Dr. George Gokel

Dr. George Gokel is a Distinguished Professor of Science and Associate Director of the Center for Nanoscience at the University of Missouri in St. Louis. (Sept. Tr. (Gokel) 334:3-8; PTX 774.) He is an expert in chemistry, including synthetic and peptide chemistry. (Sept. Tr. (Gokel) 340:4-10.)

Dr. Gokel testified regarding the chemistry described in the patents-in-suit; Defendants' infringement with regard to the claim limitations relating to copolymer-1 and the process for making copolymer-1; and provided an overall infringement

opinion. He also provided rebuttal testimony regarding the issues of non-obviousness and best mode.

Dr. Nicole Sampson

Dr. Nicole Sampson is a Professor of Chemistry at Stony Brook University. (Sept. Tr. (Sampson) 536:6-10; PTX 436.) She is an expert in peptide and polymer chemistry. (Sept. Tr. (Sampson) 542:20-25.)

Dr. Sampson testified regarding Defendants' infringement with regard to the copolymer-1 claim limitations under the doctrine of equivalents and provided rebuttal testimony on the issue of non-obviousness.

ii. Mylan's Witnesses

Dr. Walter Owens

Dr. Walter Owens is the Vice President of Global Research and Development at Mylan Inc. (Sept. Tr. (Owens) 594:8-17.) He testified regarding the development of Mylan's generic Copaxone® product, including Mylan's use of universal calibration and the testing of its proposed product on the experimental autoimmune encephalomyelitis model.
Dr. Stephen Kent

Dr. Stephen Kent is a professor of chemistry, biochemistry, and molecular biology at the University of Chicago, where he has worked for the last ten years. He is an expert in the chemical synthesis and analysis of peptides and proteins. (Sept. Tr. (Kent) 651:10-16.)

At trial, he testified regarding, among other things, Mylan's best mode defense and provided rebuttal testimony regarding Mylan's infringement with regard to the copolymer-1 claim limitations.

Dr. Allen Zeiger

At the time of his retirement in 1998, Dr. Allen Zeiger was a professor of biochemistry and molecular biology at Jefferson Medical College at Thomas Jefferson University in Philadelphia. (Sept. Tr. (Zeiger) 785:2-12; DTX 1966; DTX 4030.) As a professor, he taught gel filtration chromatography (i.e., SEC) to graduate level students for 35 years. (Sept. Tr. (Zeiger) 870:23-871:3.)

Dr. Zeiger is an expert in the fields of biochemistry, immunochemistry, synthetic peptide chemistry, peptide polymer chemistry, and in the characterization of the properties of peptide polymers. (Sept. Tr. (Zeiger) 798:4-6, 799:7-8, 798:7-13, 799:7-8, 798:14-17, 799:7-8, 798:18-20, 799:7-8, 798:21-23, 799:10-23, 870:23-871:3.) At trial, he testified regarding, among other things, Mylan's obviousness defense.

Dr. Susan Rice

Dr. Susan Rice has her own consulting firm, Susan A. Rice and Associates, Inc. (Sept. Tr. (Rice) 995:23-996:10.) She testified regarding toxicity data disclosed in the patents-in-suit, and whether the data demonstrate that the claimed copolymer-1 has unexpected results over the prior art.

Dr. Ari Green

Dr. Ari Green received his M.D. in 2001 from the University of California San Francisco, where he is now an Assistant Professor of Neurology and the Assistant Director of the Multiple Sclerosis Center. (Sept. Tr. (Green) 1354:16-23; PTX 1964.) He provided testimony regarding secondary considerations of non-obviousness.

iii. Sandoz's Witnesses

Dr. John Bishop

Dr. John Bishop is Senior Vice President, Pharmaceutical Sciences, at Momenta. (Sept. Tr. (Bishop) 1062:25-1063:5.) He testified regarding, among other things, the development of Momenta's generic Copaxone® product.

Dr. Trevor Laird

Dr. Trevor Laird is currently Owner and Senior Consultant for Scientific Update, a consultancy in the area of organic process chemistry. At trial, Dr. Laird testified regarding, among other things, Sandoz's obviousness defense and provided rebuttal testimony on Sandoz's infringement with regard to the "test reaction" claim limitations.

Dr. Carl Scandella

Since 1992, Dr. Carl Scandella has provided consulting services in the areas of biomolecule purification and analysis, process development, and manufacture of clinical lots, including the use of SEC. (Sept. Tr. (Scandella) 1169:15-18; DTX 3564.) During the course of his career, he has used a wide variety of analytical techniques for molecular weight measurement, including SEC, ultracentrifugation, MALDI-TOF mass spectrometry, and light scattering, among others. (Sept. Tr. (Scandella) 1186:17-1187:12.) Dr. Scandella is an expert on SEC and the characterization of molecular weight. (Sept. Tr. (Scandella) 1191:9-15.) At trial, he testified

regarding the Defendants' lack of enablement and indefiniteness defenses.

Dr. Randolph Wall

Dr. Randolph Wall is a Distinguished Professor in the Department of Microbiology, Immunology and Molecular Genetics at the UCLA School of Medicine and is the Associate Director of the UCLA Broad Stem Cell Center. (Sept. Tr. (Wall) 1747:15-18.) He has been a professor at UCLA since 1972. (Sept. Tr. (Wall) 1747:19-20.)

Dr. Wall is an expert in SEC. (Sept. Tr. (Wall) 1756:16-20; 1761:18.) At trial, he was a rebuttal witness for Sandoz regarding its lack of enablement and indefiniteness defenses,

iv. Witnesses Testifying by Deposition

The parties submitted designated deposition testimony from several witnesses including the following: Weizmann employees Professor Ruth Arnon and Dr. Michael Sela; current or former Teva employees Dr. Irit Pinchasi, Eliezer Konfino, Dr. Alexander Gad, and Dr. Haim Varkony; Mylan employees Dr. Stephen Wayne Talton and Dr. Ross Wallingford; Natco employees Dr. Bhujanga Rao, Dr. Duddhi Linga Rao, and Dr. Satyanarayana Kota; current or former Momenta employees Dr. Corinne Bauer, Dr. Steve Brugger, Dr. Ganesh Venkataraman, and Dr. Mani Iyer; Sandoz employees Dr. Anup Ray and Shrinvasa Rao; and Defendants' expert witnesses Dr. Jerard Hurwitz

(Mylan) and Dr. Frantisek Svec (Sandoz). None of these witnesses testified at the September trial.

IV. The Patents-in-Suit and the Patent Claims at Issue

Prior to the September trial, Plaintiffs voluntarily limited the number of asserted claims to narrow the issues for trial. The asserted claims of the patents-in-suit are claim 1 of the '808 patent; claim 1 of the '589 patent; claims 1, 2, and 3 of the '898 patent; claims 1, 2, and 3 of the '430 patent; claim 1 of the '476 patent; claim 1 of the '161 patent; claims 1 and 6 of the '847 patent; claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent; and claims 1 and 8 of the '098 patent. Plaintiffs assert claim 3 of the '430 patent and claim 3 of the '898 patent against Mylan only.

The asserted claims claim, among other things, copolymer-1 with lower molecular weight characteristics, methods of making lower molecular weight copolymer-1, pharmaceutical compositions comprising lower molecular weight copolymer-1, as well as methods of treating multiple sclerosis using the claimed lower molecular weight copolymer-1. The asserted claims contain limitations relating generally to one or more of the molecular weight attributes of the claimed copolymer-1, the process for making the claimed copolymer-1, and the use of the claimed copolymer-1 for treating multiple sclerosis.

A. Molecular Weight Claim Limitations

All but three of the 22 asserted claims of the patents-in-suit include numerical limitations

directed to molecular weight attributes of either the copolymer-1 end product and/or an intermediate product called trifluoroacetyl ("TFA") copolymer-1. The molecular weight limitations can be categorized as "average molecular weight" and "molar fraction" limitations. (PTX 1-2; PTX 4-9.) In addition, three of the asserted claims are directed to a "predetermined molecular weight profile" and have no numerical limitations. (PTX 3.)

i. Average Molecular Weight Limitations

Claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1 and 6 of the '847 patent and claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent are directed to copolymer-1 having an "average molecular weight" falling within a particular numeric range. (PTX 1; PTX 2; PTX 7; PTX 8.) For example, claim 1 of the '539 patent provides:

> A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has **an average molecular weight of about 4 to about 9 kilodaltons,** wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence, and wherein the composition is suitable for treating multiple sclerosis.

(PTX 8 at 5:18-24 (emphasis added).)

The asserted claims containing "average molecular weight" limitations require copolymer-1 having an average molecular weight of "about 5 to 9

kilodaltons" (claim 1 of the '808 patent and claim 1 of the '589 patent), "about 4 to about 9 kilodaltons" (claims 1 and 6 of the v847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the '539 patent), and "6.25 to 8.4 kilodaltons" (claim 10 of the '539 patent). (PTX 1; PTX 2; PTX 7; PTX 8.)

ii. Molar Fraction Limitations

Several of the asserted claims include limitations relating to the molecular weight distribution of a sample of copolymer-1 or the intermediate TFA copolymer-1. These "molar fraction" limitations are expressed as a certain percentage of the copolymer-1 polypeptides (or TFA copolymer-1 molecules) having molecular weights falling within a molecular weight range or above a particular molecular weight value. (PTX 4; PTX 5; PTX 6; PTX 8; PTX 9.) Claim 1 of the '430 patent exemplifies the copolymer-1 molar fraction and TFA copolymer-1 molar fraction limitations:

> Copolymer-1 having **over 75% of its molar fraction within the molecular weight range from about 2 kDa** to about 20 kDa, prepared by a process comprising the steps of:
>
> reacting protected copolymer-1 with hydrobromic acid to form **trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa** to about 20 kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight

> range from about 2 kDa to about 20 kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa.

(PTX 4 at 5:21-6:8 (emphasis added).)

The copolymer-1 "molar fraction" limitations include "over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" (claims 1, 2, and 3 of the '430 patent); "less than 2.5% .. over 40 kilodaltons" (claims 8 and 30 of the '539 patent); "less than 5% ... over 40 kilodaltons; and ... over 75% ... within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons" (claim 1 of the ' 476 patent; claim 1 of the '161 patent; claim 1 of the '098 patent); and "less than 2.5% .. above 40 kDa" (claims 9, 10, and 31 of the '539 patent and claim 8 of the '098 patent). (PTX 4; PTX 5; PTX 6; PTX8; PTX9.)

All of the TFA copolymer-1 molar fraction limitations require "trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa" (claims 1, 2, and 3 of the '430 patent; claim 1 of the '476 patent; claim 1 of the '161 patent). (PTX 4; PTX 5; PTX 6.)

iii. Predetermined Molecular Weight Profile Limitations

Claims 1, 2 and 3 of the '898 patent do not include any numerical molecular weight limitations. Instead, they require that the copolymer-1 have a

"predetermined molecular weight profile." (PTX 3.) For example, claim 1 of the '898 patent provides:

> A method of manufacturing co**polymer-1 of a predetermined molecular weight profile**, comprising the steps of: selecting a predetermined molecular weight profile, reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having the predetermined molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and treating said trifiuoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile.

(PTX 3 at 5:35-6:11 (emphasis added).)

B. Process Limitations

Twelve of the asserted claims are directed either to a method of manufacturing copolymer-1 having the desired molecular weight characteristics or to copolymer-1 that is made by a particular process. Although the details of each claim may vary, claim 1 of the '589 patent is illustrative of the claims directed to a process for making the claimed copolymer-1:

> Copolymer-1 having a molecular weight of about 5 to 9 kilodaltons, **made by a process** comprising the steps of:
>
> reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl

> copolymer-1, treating said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.

(PTX 2 at 6:4-13 (emphasis added).)

The asserted process for making and product-by-process claims are claim 1 of the '808 patent; claim 1 of the '589 patent; claims 1, 2, and 3 of the '898 patent; claims 1, 2, and 3 of the '430 patent; claim 1 of the '476 patent; claim 1 of the '161 patent; and claims 1 and 6 of the '847 patent. Claims 1, 2, and 3 of the '898 patent; claims 1, 2, and 3 of the '430 patent; claim 1 of the '476 patent and claim 1 of the '161 patent also require that the hydrogen bromide ("HBr") treatment step "take[] place for a time and at a temperature predetermined by test reaction." (PTX 3; PTX 4; PTX 5; PTX 6.)

C. Treatment of Multiple Sclerosis

Ten of the asserted claims include limitations relating to the treatment of multiple sclerosis. Claim 1 of the '476 patent and claims 23, 30, and 31 of the '539 patent are directed to methods for treating multiple sclerosis. Claim 1 of the '161 is directed to "[a] composition for the treatment of multiple sclerosis." Claims 1, 8, 9, and 10 of the '539 patent recite "wherein the composition is suitable for treating multiple sclerosis." Claim 12 of the '539 patent recites "a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition." (PTX 5; PTX 6; PTX 8.)

D. Pharmaceutical Composition

Four of the asserted claims include limitations relating to the use of the lower molecular weight copolymer-1 as a pharmaceutical composition. Claims 12, 23, 30, and 31 of the '539 patent are directed to the use of lower molecular weight copolymer-1 as a pharmaceutical composition. (PTX 8.) For example, claim 12 of the '539 provides:

> A pharmaceutical composition comprising:
>
> a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition, wherein the copolymer-1 composition comprises a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence; and a pharmaceutically acceptable excipient.

(PTX 8 at 5:54-63.)

V. Copolymer-1 and Multiple Sclerosis

A. Multiple Sclerosis: The Disease

Multiple sclerosis is an inflammatory disease of the central nervous system first recognized in the 1860s by the French neurologist Jean-Martin Charcout. (See Sept. Tr. (Lisak) 88:8-89:18.) It is an unpredictable disease involving two of the most complex systems in the body—the immune system and the central nervous system. (Sept. Tr. (Lisak)

136:3-10.) In persons afflicted with multiple sclerosis, autoimmune cells attack myelin, a protective sheath wrapped around nerves found in the brain and the spinal cord. (Sept. Tr. (Lisak) 88:8-89:4.) This leads to the degeneration of myelin and, eventually, the degeneration or death of underlying nerve cells. (Sept. Tr. (Lisak) 90:4-92:11.)

This degeneration process eventually prevents the central nervous system from functioning properly as the brain loses the ability to send or receive messages to and from various parts of the body and as other functions of the brain or spinal cord become impaired. (Sept. Tr. (Lisak) 90:4-92:11.) As multiple sclerosis progresses, the immune system's attack on myelin causes multiple lesions or scars to form on the brain and the spinal cord. (Sept. Tr. (Lisak) 89:11-15.) The appearance of these multiple scars or scleroses accounts for the disease name "multiple sclerosis." (Sept. Tr. (Lisak) 89:11-15.)

The most common form of multiple sclerosis is RRMS. (Sept. Tr. (Lisak) 96:17-19.) Approximately 85% of all multiple sclerosis patients have this form of the disease. (Sept. Tr. (Lisak) 89:11-15.) Patients with RRMS experience periodic relapses or attacks which are accompanied by steadily worsening disability as the functioning of the nervous system becomes more impaired over time. (Sept. Tr. (Lisak) 95:16-96:25.) The symptoms of RRMS include blurred and double vision, loss of balance and coordination, tremors, fatigue, bladder and bowel dysfunction, paralysis, and even death in some patients. (Sept. Tr. (Lisak) 92:20-93:21.) Patients may exhibit different neurologic symptoms at

various times and many patients become permanently disabled. (Sept. Tr. (Lisak) 92:20-93:21.)

The initial onset of multiple sclerosis typically occurs early in life—between the ages of twenty and forty. (Sept. Tr. (Lisak) 94:10-18.) Dr. Lisak testified that the disease strikes patients in the "prime of life"—when they are beginning their careers, finishing school, or beginning to raise a family. (Sept. Tr. (Lisak) 94:10-18.) There is no way to predict when relapses associated with multiple sclerosis will occur and thus the disease acts like a "hanging sword," threatening sufferers with future attacks of unknown length that may result in increased or complete disability. (Sept. Tr. (Lisak) 97:1-9.)

Prior to the 1990s, there were no treatments available to prevent relapses or slow the progression of disability associated with the disease. (Sept. Tr. (Lisak) 102:2-9; Sept. Tr. (Green) 1391:21-1392:4.) The only option for a physician was to treat a patient's symptoms and to try to shorten the duration of a relapse. (Sept. Tr. (Lisak) 102:2-9; Sept. Tr. (Green) 1391:21-1392:4.)

B. The Weismann Scientists' Discovery of Copolymer-1

Professor Arnon, Professor Sela, and Dr. Teitelbaum are Ph.D. immunologists who worked together at Weizmann, a world-renowned research institute located in Israel. (July Tr. (Pinchasi) 9:12-20; 16:11-17:5; July Tr. (Arnon) 302:23-303:13, 304:11-17; 304:18-305:14.) In about 1966, Professor

Arnon and her colleagues became interested in studying an autoimmune disease called experimental autoimmune encephalomyelitis ("EAE"), which is an animal model for multiple sclerosis. (July Tr. (Arnon) 309:11-310:10.) It was already understood by that time that EAE was induced by a single protein called myelin basic protein ("MBP"), but nothing was known about the mechanism of the disease. (July Tr. (Arnon) 309:11-310:10.) Professor Arnon and her colleagues theorized that if they could produce a synthetic polymer that mimicked MBP, it could be used as a research tool to study the mechanism of EAE. (July Tr. (Arnon) 309 : 11-311:8.)

Professor Arnon and her colleagues synthesized three synthetic polymers, which they called copolymer-1, copolymer-2, and copolymer-3. The copolymers differed in their amino acid composition, but were all targeted to have a molecular weight of 23,000 daltons, which was the molecular weight of MBP. (July Tr. (Arnon) 310:11-311:8.) Professor Arnon and her colleagues tried without success for over a year to use the synthetic copolymers to induce EAE in animals. (July Tr. (Arnon) 310:11-39 23.) Eventually, it occurred to them that the synthetic copolymers they made were not similar enough to MBP to induce EAE, but might be similar enough to MBP to compete with it and prevent its activity. (July Tr. (Arnon) 310:11-23.) The experiments they set up to test their hypothesis were successful. (July Tr. (Arnon) 310:11-23.) Instead of inducing EAE, copolymer-1 proved to be effective in suppressing EAE, (July Tr. (Arnon) 310:24-311:13.) The other two copolymers were much less effective. (July Tr. (Arnon) 311:9-13.)

At the time Professor Arnon and her colleagues discovered that copolymer-1 was effective in suppressing EAE, there were practically no treatments available for multiple sclerosis. (July Tr. (Arnon) 311:14-23.) The only options for patients were immunosuppressive drugs, but these had very severe side effects and were not routinely used. (July Tr. (Arnon) 311:14-23.)

Professor Arnon and her colleagues published their initial findings in 1971 in the European Journal of Immunology ("1971 Teitelbaum article"). (PTX 499.) The article described copolymer-1 as having a molecular weight of 23,000 daltons. (July Tr. (Arnon) 311:24-312:22; PTX 499 at 242.)

In 1974, the PTO granted U.S. Patent No. 3,849,550 (the '550 Patent") to Yeda. (DTX 1219.) The patent named Professor Arnon, Professor Sela, Dr. Teitelbaum, and their co-workers as inventors, and disclosed and claimed the copolymers that they discovered could treat EAE. (DTX 1219.)

The first placebo controlled clinical study of copolymer-1 for the treatment of multiple sclerosis was conducted by Professor Murray Bornstein of the Albert Einstein College of Medicine in New York ("Bornstein trial"). (July Tr. (Arnon) 316:6-15; July Tr. (Pinchasi) 22:4-24; Sept. Tr. (Lisak) 108:25-104:13.) Fifty patients were enrolled in the pilot trial, 25 of whom received copolymer-1. (Sept. Tr. (Lisak) 109:24-110:4; PTX 31 at 408.) Professor Arnon and her colleagues at Weizmann participated in the basic design of the Bornstein trial and supplied Dr. Bornstein with copolymer-1 for use in

the trial. (July Tr. (Arnon) 316:16-21.) The copolymer-1 they supplied was intended to have a molecular weight of 23,000 daltons in order to match the molecular weight of MBP. (July Tr. (Arnon) 316:22-317:11.) In fact, however, the batches ranged from 14,000 to 23,000 daltons. (July Tr. (Arnon) 317:12-15; Sept. Tr. (Lisak) 110:11-21; PTX 31 at 408.)

The results of the Bornstein trial were published in 1987 in the New England Journal of Medicine ("1987 Bornstein article"). (July Tr. (Arnon) 327:22-328:9; Sept. Tr. (Lisak) 108:25-109:13; PTX 31.) While the results from the study were encouraging, they did not definitively establish whether the copolymer-1 composition studied was a safe and effective treatment for RRMS. (PTX 31 at 408; Sept. Tr. (Lisak) 108:25-111:22.)

During the Bornstein trial, Dr. Bornstein notified Professor Arnon and her colleagues that some of the patients experienced local injection site reactions and that, on rare occasions, some patients experienced systemic side effects that included difficulty breathing, palpitations, severe flush, sweating, and severe anxiety. (July Tr. (Arnon) 317:16-320:6; July Tr. (Pinchasi) 23:17-24:23; PTX 28.) His report of these side effects was of grave concern to Professor Arnon. (July Tr. (Arnon) 320:7-16.) She knew copolymer-1 was to be given to patients on a daily basis and, as a result, that any side effects would be a severe issue. (July Tr. (Arnon) 320:7-16.) At that time, however, neither Professor Arnon nor her colleagues had any idea what was causing the side

effects or how they could get rid of them. (July Tr. (Arnon) 320:7-16.)

Based on Dr. Bornstein's reports, Professor Arnon and her colleagues looked for screening assays that could be used to differentiate between batches that would cause side effects and those that would not. (July Tr. (Arnon) 320:17-25.) They eventually utilized the in vitro RBL degranulation test. (July Tr. (Arnon) 320:17-25; DTX 3114.) In the RBL degranulation test, RBL cells are preloaded with radio-labeled serotonin and then exposed to copolymer-1. (July Tr. (Arnon) 327:8-21; July Tr. (Baird) 587:3-589:20.) The amount of serotonin released, or degranulated, by the cells is then measured. (July Tr. (Arnon) 327:8-21; July Tr. (Pinchasi) 25:11-26:1; July Tr. (Baird) 587:3-589:20; DTX 3114.) The RBL test was and still is used as a model for allergic-type reactions, because the degranulation it exhibits in the presence of a stimulant mimics the immune response of human mast cells—a central cell in the allergic immune response system—in responding to allergens or other substances. (July Tr. (Arnon) 321:8-18, 322:21-323:4; July Tr. (Baird) 576:24-577:7, 578:16-582:16, 585:9-21; PTX 522.)

The Weizmann scientists adopted the term "toxicity" to refer to the results of the RBL degranulation test. (July Tr. (Arnon) 327:8-21.) If 30% or more serotonin was released upon exposure to copolymer-1, the batch was designated "toxic" and discarded. (July Tr. (Arnon) 327:8-330:18; PTX 31 at 409.)

One of Professor Arnon's colleagues at Weizmann who was very experienced with the RBL degranulation test suggested the test. (July Tr. (Arnon) 321:8-18.) Before making the decision to go forward with the RBL degranulation test, Professor Arnon personally read all of the literature about the test, including articles by Dr. Reuben Siraganian's group at NIH. (July Tr. (Arnon) 321:8-18, 322:21-323:4; July Tr. (Baird) 576:24-577:7, 578:16-582:16, 585:9-21; PTX 522.)

C. Teva's Agreement with Weizmann

In November 1987, Teva and Yeda, the commercial arm of Weizmann, entered into an agreement for the development of copolymer-1. (DTX 1232.) Teva's goal was to take the invention made by the Weizmann scientists and translate it into a useful pharmaceutical product that could be given to multiple sclerosis patients. (July Tr. (Pinchasi) 12:10-16.) The copolymer-1 project at Teva was divided into chemical, analytical, pharmaceutical, and biological development teams, which were responsible for different aspects of the project. (July Tr. (Pinchasi) 15:4-18.)

Dr. Pinchasi served as project manager of the copolymer-1 project at Teva and was responsible for coordinating all development work. (July Tr. (Pinchasi) 11:6-12, 14:12-15:3.) At trial, Dr. Pinchasi testified that because she is not a chemist, she had only high-level managerial responsibility for the chemical, analytical, and pharmaceutical aspects of the project. (July Tr. (Pinchasi) 15:4-16:3.) She had

more substantive input into the biological aspects of the project. (July Tr. (Pinchasi) 14:12-16:3.)

The biology team consisted of Dr. Pinchasi, and Professor Arnon and Dr. Teitelbaum from Weizmann. (July Tr. (Pinchasi) 16:4-18.) Dr. Pinchasi met frequently with both Professor Arnon and Dr. Teitelbaum, and worked in Dr. Teitelbaum's laboratory for several months. (July Tr. (Pinchasi) 16:19-17:5.) Although Professor Arnon was involved at a higher level, she was consulted on all significant decisions. (July Tr. (Pinchasi) 16:19-17:5.)

When Dr. Pinchasi began working on the project, she understood from Weizmann scientists that copolymer-1 needed to have a molecular weight in the range of MBP, which was about 20,000 daltons. (July Tr. (Pinchasi) 18:6-19:1, 33:12-14 ("They were actually aiming at 23,000 daltons, which is the molecular weight of myelin basic protein, the endogenous protein copolymer-1 was designed to mimic.").) In fact, in 1974, Professor Arnon and her colleagues published an abstract in the Israeli Journal of Medical Sciences ("1974 Teitelbaum abstract") that reported that copolymers having the same composition as copolymer-1 but with molecular weights lower than 17,000 or higher than 50,000 daltons proved ineffective for suppression of EAE. (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:4; PTX 509 at 1172-73.) Dr. Pinchasi also learned that the molecular weight of the copolymer-1 used in the Bornstein trial ranged from 14,000 to 23,000 daltons. (July Tr. (Pinchasi) 22:4-21, 33:21-34:5.)

For these reasons, at the beginning of the copolymer-1 project, Teva aimed to produce a high molecular weight copolymer-1, in the range of 20,000 daltons. (July Tr. (Pinchasi) 18:6-19:1, 33:6-34:5.)

Early on in the copolymer-1 project, Dr. Pinchasi and her team were informed about the local and systemic side effects Dr. Bornstein observed in his clinical trial. (July Tr. (Pinchasi) 24:2-23.) They learned that Weizmann scientists concluded that these side effects were caused by something "toxic" in the copolymer-1 batches, but that Professor Arnon and her colleagues had no idea what that toxic element was. (July Tr. (Pinchasi) 24:24-25:10.) Dr. Pinchasi and her team also learned Weizmann scientists had developed the RBL degranulation test in order to screen batches for "toxicity." (July Tr. (Pinchasi) 25:11-26:18.)

Solving the toxicity problem was one of the initial major challenges the Teva and Weizmann scientists faced in developing copolymer-1 into a pharmaceutical product. Much of their development work was focused on this issue. (July Tr. (Pinchasi) 26:19-27:6; July Tr. (Arnon) 331:7-333:6.) The Teva and Weizmann scientists studied the literature for clues as to what might be causing the toxicity and investigated many different possibilities. (July Tr. (Pinchasi) 26:19-27:6.) In the end, the literature did not provide an answer. (July Tr. (Pinchasi) 26:19-27:19.)

Finally, the Teva and Weizmann scientists discovered that toxicity—the cause of the side effects Dr. Bornstein observed during his clinical trial—was

related to the molecular weight of the product. (July Tr. (Pinchasi) 27:25-28:25.) The higher the average molecular weight of a copolymer-1 batch, the higher the probability that the batch would be toxic. (July Tr. (Pinchasi) 27:25-28:25; July Tr. (Arnon) 332:8-333:6; DTX 3567 (Konfino Dep. Tr. Vol. 1) at 62:24-63:9.) In particular, they discovered that there was a narrow molecular weight range between 5,000 and 9,000 daltons in which there is a high probability that a copolymer-1 batch will be both active and non-toxic. (July Tr. (Arnon) 333:7-17; July Tr. (Pinchasi) 34:6-35:5.)

Teva initially determined toxicity using Weizmann's RBL degranulation test. (July Tr. (Pinchasi) 29:1-5.) It later added an in vivo toxicity test in which copolymer-1 is injected into mice. (July Tr. (Pinchasi) 29:1-13.)

The correlation between molecular weight and toxicity that was discovered by the Teva and Weizmann scientists was unexpected. (July Tr. (Pinchasi) 32:1-6, 34:19-35:5; July Tr. (Arnon) 333:23-334:2.) There was nothing in the literature that indicated such a correlation. (July Tr. (Pinchasi) 32:1-6.) It was also unexpected that copolymer-1 in the range of 5,000 to 9,000 daltons would be both non-toxic and active. The Teva and Weizmann scientists believed that a much higher molecular weight was needed for copolymer-1 to have activity because copolymer-1 was meant to mimic MBP, with a molecular weight in the range of 20,000 daltons, and because Weizmann's previous testing showed lower molecular weight copolymer-1 to be ineffective.

(July Tr. (Pinchasi) 33:6-34:5, 34:19-35:5; July Tr. (Arnon) 312:23-313:18, 316:25-317:11, 333:18-22.)

To obtain regulatory approval to market copolymer-1 in the United States, Teva needed to submit two pivotal studies on copolymer-1 to the FDA. The two pivotal studies are supposed to be performed with exactly the same product, having exactly the same characteristics. (July Tr. (Pinchasi) 35:12-36:20, 37:18-38:4.) Teva planned to rely on the Bornstein trial as one of its two pivotal studies. As explained earlier, however, the Bornstein trial used copolymer-1 having a molecular weight between 14,000 and 23,000 daltons. (July Tr. (Pinchasi) 35:18-21, 37:2-14.) Because of the toxicity issues that had been discovered, Teva knew it would have to perform its second pivotal study with much lower molecular weight copolymer-1. Teva understood that the FDA might not accept the Bornstein trial as one of the two pivotal studies if it switched to the lower molecular weight copolymer-1, and that it might therefore have to perform a second trial before copolymer-1 would be approved. (July Tr. (Pinchasi) 37:15-38:4.) For these reasons, Teva had an "up front" meeting with the FDA, where they shared "the data that was available for copolymer-1." (July Tr. (Pinchasi) 37:5-8, 38:3-4.)

In addition to its regulatory concern, from a practical perspective, Teva understood it would be a challenge to reproducibly produce copolymer-1 having a molecular weight of 5,000 to 9,000 daltons because the Teva and Weizmann scientists had not yet developed a manufacturing process that could

sufficiently control the molecular weight of the final product. (July Tr. (Pinchasi) 38:14-39:4.)

To avoid marketing a product that had a chance of being toxic, Teva targeted a molecular weight for copolymer-1 of about 7,000 daltons. (July Tr. (Pinchasi) 38:5-39:4, 81:13-82:19; PTX 708 at TEV000324552.) Teva's second pivotal trial began in October 1991. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597 at 1271.) This clinical trial, named the Johnson Study after principal investigator Kenneth Johnson, was a Phase III large-scale, multicenter, placebo-controlled, double-blinded study. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597 at 1268.) A total of 251 patients participated in the two-year trial. (Sept. Tr. (Lisak) 106:24-108:17; PTX 597.)

The study demonstrated, for the first time, that copolymer-1 was a safe and effective treatment for patients with RRMS. (Sept. Tr. (Lisak) 110:22-111:22.) It also demonstrated, among other things, that daily injections of copolymer-1 resulted in a statistically significant reduction in relapse rates for patients with RRMS. (Sept. Tr. (Lisak) 107:25-108:4; PTX 597 at 1268.) The study concluded in 1994 and the results were published in 1995 in the Journal of Neurology. (PTX 597.)

On June 14, 1995, Teva submitted its NDA, relying on both the 1987 Bornstein trial and the Johnson Study to demonstrate the safety and efficacy of copolymer-1. (PTX 81 at TEV000002326.) While Teva represented to the FDA that the safety of the copolymer-1 compositions studied in the Johnson Study and the Bornstein trial were comparable, Teva

did not draw any comparisons between the tolerability of the compositions or their propensity to cause injection site reactions. (PTX 881 (Green Dep.) at 111:11-18; PTX 81.)

Although Teva's NDA set an average molecular weight specification of 4,700 to 13,000 daltons, Teva actually targeted an average molecular weight of 7,000 + 1,000 daltons for the batches of copolymer-1 that were to be marketed. (July Tr. (Pinchasi) 85:23-89:22.) Teva informed the FDA of this 7,000 ± 1,000 daltons average molecular weight target as part of its NDA submission. (July Tr. (Pinchasi) 85:23-89:22; DTX 1023 at TEV000000455; see also July Tr. (Pinchasi) 81:23-85:13; PTX 723 at TEV000599260.) Teva set the formal specification at 4,700 to 13,000 daltons originally to maintain a larger margin for average molecular weight in light of potential manufacturing changes that might be necessary to market the product. (July Tr. (Pinchasi) 86:4-86:24.) Batches within the 4,700 to 13,000 daltons specification were still tested for toxicity on the RBL screen and in vivo mouse test, and rejected if they failed on either of those screens. (July Tr. (Pinchasi) 86:4-24.)

D. Discovery of the Process for Achieving Low Molecular Weight Copolymer-1

Teva was able to reproducibly achieve the narrow molecular weight range of about 7,000 daltons because of a discovery made by Teva chemist Eliezer Konfino. When Teva scientists began working on the copolymer-1 project, they found that the same

starting materials and what they believed to be the same reaction conditions produced copolymer-1 of varying molecular weights. (July Tr. (Pinchasi) 38:14-39:4.) Konfino discovered that the second step of the process for making copolymer-1, which involves the addition of HBr/acetic acid, cleaves, or cuts up, the polypeptide copolymer-1 chains, and therefore lowers the average molecular weight of the product. (July Tr. (Pinchasi) 68:5-25, 76:13-77:18, 81:23-85:13; PTX 36; PTX 36-T; PTX 42.)

Konfino found that he could control the average molecular weight of the final copolymer-1 product by controlling the time and temperature of the second step of the process. The longer the reaction is run, and the higher the temperature, the more cleavage occurs and the lower the average molecular weight of the product. (July Tr. (Pinchasi) 68:5-25, 76:13-77:18, 81:23-85:13; PTX 36; PTX 36-T; PTX 42.) Konfino also discovered that the time and temperature for the Step 2 reaction that would provide copolymer-1 of approximately 7,000 daltons could be determined by running a test reaction. (July Tr. (Pinchasi) 81 :23-82:19.)

VI. Background on Polypeptide Chemistry, Synthesis, Analytical Testing

A. Polypeptide Chemistry

A polymer is a molecule composed of smaller subparts called monomers. (Sept. Tr. (Grant) 191:9-16; PTX 986 at 4.) A copolymer is a polymer composed of more than one type of monomer. (Sept. Tr. (Grant) 191:19-192:1; PTX 986 at 4.) The

monomers that make up copolymer-1 are amino acids. (Sept. Tr. (Grant) 192:2-3.) An amino acid is a molecule that contains an amino group, a carboxylic acid group, and a side chain. (Sept. Tr. (Grant) 192:4-19; Sept. Tr. (Gokel) 341:6-25; PTX 986 at 5; PTX 987 at 4.)

A polypeptide is a molecule made up of amino acid monomers that are joined together by peptide bonds. (Sept. Tr. (Grant) 180:17-21; Sept. Tr. (Gokel) 344:11-22.) Copolymer-1 is a mixture of polypeptides. (PTX 1 at 1:32.) The polypeptides comprising copolymer-1 are synthetic (i.e., they are made in a laboratory) and they are composed of four amino acids: glutamic acid, lysine, alanine, and tyrosine. (Sept. Tr. (Grant) 180:22- 23, 183:13-19, 192:20-193:23; Sept. Tr. (Gokel) 342:12-344:10, 344:23-345:12; PTX 986 at 6-7; PTX 987 at 6, 8-11.)

The individual polypeptide molecules, or "species," in copolymer-1 have different lengths and sequences. For that reason, the molecular weight of a sample of copolymer-1 can best be described either as an average molecular weight or as a molecular weight distribution. (Sept. Tr. (Grant) 194:14-195:2, 195:7-10, 1544:23-1545:11; Sept. Tr. (Scandella) 1193:24-1194:2; PTX 986 at 8.) The molecular weight of an individual polypeptide molecule is the sum of the atomic weights of the atoms comprising the molecule. (Sept. Tr. (Grant) 193:24-194:13.) A molecular weight distribution, by contrast, is a description of the molecular weights of the polypeptides that make up a mixture of polypeptide molecules. (Sept. Tr. (Grant) 198:9-13.)

B. Synthesis of Copolymer-1

The varying lengths and sequences of the polypeptide chains in a sample of copolymer-1 are a result of the method of its synthesis. (Sept. Tr. (Grant) 195:11-197:10.) The patents-in-suit teach that copolymer-1 is synthesized using a four-step process in a "batch" method of synthesis. (Sept. Tr. (Gokel) 352:2-354:15; Sept. Tr. (Grant) 1401:19-1402:4; PTX 1 at 4:30-6:3; PTX 987 at 22.)

In Step 1, the N-carboxyanhydrides, or activated versions, of the amino acids glutamic acid, lysine, alanine, and tyrosine are combined in the presence of a chemical called an initiator. The initiator starts the reaction of the amino acids by joining with one of the activated amino acids, which removes the N-carboxyanhydride group and allows the first amino acid to join to a second amino acid, which in turn allows the second amino acid to react with a third amino acid, and so forth. Each initiator molecule starts a new polypeptide chain. This sequence of reactions results in polymerization of the amino acids into polypeptide chains. (Sept. Tr. (Grant) 195:17-197:16; Sept. Tr. (Gokel) 349:3; PTX 986 at 9; PTX 987 at 14.)

Glutamic acid and lysine each have two sites that can form bonds with other amino acids. In order to ensure that the amino acids combine with each other in a straight chain and do not become branched during the polymerization step, protecting groups are used to block the reactive sites on the side chain of each of these amino acids. Benzyl groups are used to protect the glutamic acid and TFA groups are used

to protect the lysine. (Sept. Tr. (Gokel) 342:16-343:23, 345:5-346:25; PTX 987 at 7, 12-13.) The result of the Step 1 polymerization is called "protected copolymer-1" because the side chains of glutamic acid and lysine are protected by the benzyl and TFA protecting groups, respectively. Protected copolymer-1 is a mixture of polypeptides that have different lengths and amino acid sequences. (Sept. Tr. (Grant) 195:17-197:16; Sept. Tr. (Gokel) 347:1-349:8, 353:4-16; PTX 987 at 15, 22.)

In Step 2, the protected copolymer-1 is treated with HBr/acetic acid to remove the benzyl protecting groups from glutamic acids ("deprotection"). During the deprotection process, the polypeptide chains are also cleaved ("depolymerized"), which results in shorter polypeptide chains. (Sept. Tr. (Gokel) 347:1-350:5, 353:17-25; PTX 987 at 16-18, 22.) The resulting product of the Step 2 deprotection/depolymerization process is called TFA copolymer-1 because the TFA protecting groups remain on the lysine residues. (Sept. Tr. (Gokel) 350:11-18.)

The time and temperature of the HBr/acetic acid reaction of Step 2 determines the extent of cleavage of the polypeptide chains and the resulting average molecular weight of the copolymer-1 product. (PTX 1 at 4:59-65.) The longer the reaction is run or the higher the temperature, the more cleavage occurs and the lower the average molecular weight of the product. As a result, this step is used to control the molecular weight of the resulting copolymer-1. (Sept. Tr. (Sampson) 1641:6-1642:8; PTX 992 at 6-7; July

Tr. (Pinchasi) 81:23-82:19; DTX 1023 at TEV000000455.)

In Step 3 of the synthetic process, the TFA copolymer-1 is treated with piperidine to remove the TFA protecting groups from the lysines, resulting in copolymer-1. (Sept. Tr. (Gokel) 350:19-22, 351:3-12, 354:1-9; PTX 987 at 15, 22.) The chain lengths of the polypeptides are not affected in the TFA deprotection step. (Sept. Tr. (Gokel) 350:23-351:2.)

In Step 4 of the synthetic process, the copolymer-1 can be purified by dialysis. In one method of dialysis, acetic acid is used. (Sept. Tr. (Gokel) 350:23-351:2; PTX 1 at 5:12-6:2; PTX 987 at 22.)

C. Size Exclusion Chromatography

The patents-in-suit explicitly identify SEC as the method to be used for determining the molecular weight of copolymer-1. (Sept. Tr. (Grant) 186:16-20, 197:17-25, 326:15-18; Sept. Tr. (Scandella) 1227:5-10; PTX 1 at 3:6-7.) SEC—also known as "gel filtration" or "gel permeation chromatography"—is a separation and analytical technique that separates molecules based upon their size in solution. SEC can be used to determine the molecular weights of samples, such as polypeptides, as well as their molecular weight distributions. (Sept. Tr. (Grant) 186:5-15, 186:21-187:4, 198:1-3, 198:14-20, 329:14-20, 1411:2-5, 1415:8-17; PTX 553 at 63-64; PTX 566 at 2.)

SEC was first described in the literature in the late 1950s or early 1960s, and the first commercial SEC instrument was marketed in 1964. (Sept. Tr. (Grant)

1409:17-19; PTX 553 at 63-64; PTX 514 at 199.) By 1994, there was a considerable amount of scientific literature describing the use of SEC. (Sept. Tr. (Grant) 1409:17-23; Sept. Tr. (Scandella) 1314:15-25.) This literature included textbooks, individual book chapters, and numerous scientific articles. (Sept. Tr. (Grant) 1409:24-1410:2.) For example, N.C. Billingham, Molar Mass Measurements in Polymer Science (John Wiley & Sons 1977) ("Billingham 1977"), contains a chapter entitled "Gel Permeation Chromatography," which states that "[t]he idea of producing separation of discrete molecular species on the basis of differences in molecular size has been familiar to the biochemist for many years." (PTX 514 at 199.)

Polypeptides were some of the first substances studied by SEC, and by 1994, the prior art with respect to using SEC to determine the molecular weight of polypeptides was extensive. (Sept. Tr. (Grant) 1410:3-9.) By 1994, all aspects of the SEC process—including its theory and practice, and the interpretation of results—had been described in numerous book chapters such as Billingham 1977, the "Gel Filtration" chapter in Protein Purification - Principles, High Resolution Methods and Applications (Jan-Christer Janson and Lars Ryden eds., 1989) ("Janson 1989"), and the "Characterization of Complex Polymers by Size Exclusion Chromatography and High-Performance Liquid Chromatography" chapter from Modern Methods of Polymer Characterization (Howard G. Barth and Jimmy W Mays, 1991) ("Barth 1991"). (Sept. Tr. (Grant) 1410:10-1412:5, 1414:8-21, 1418:19-1419:21; PTX 514; PTX 553; PTX 566.)

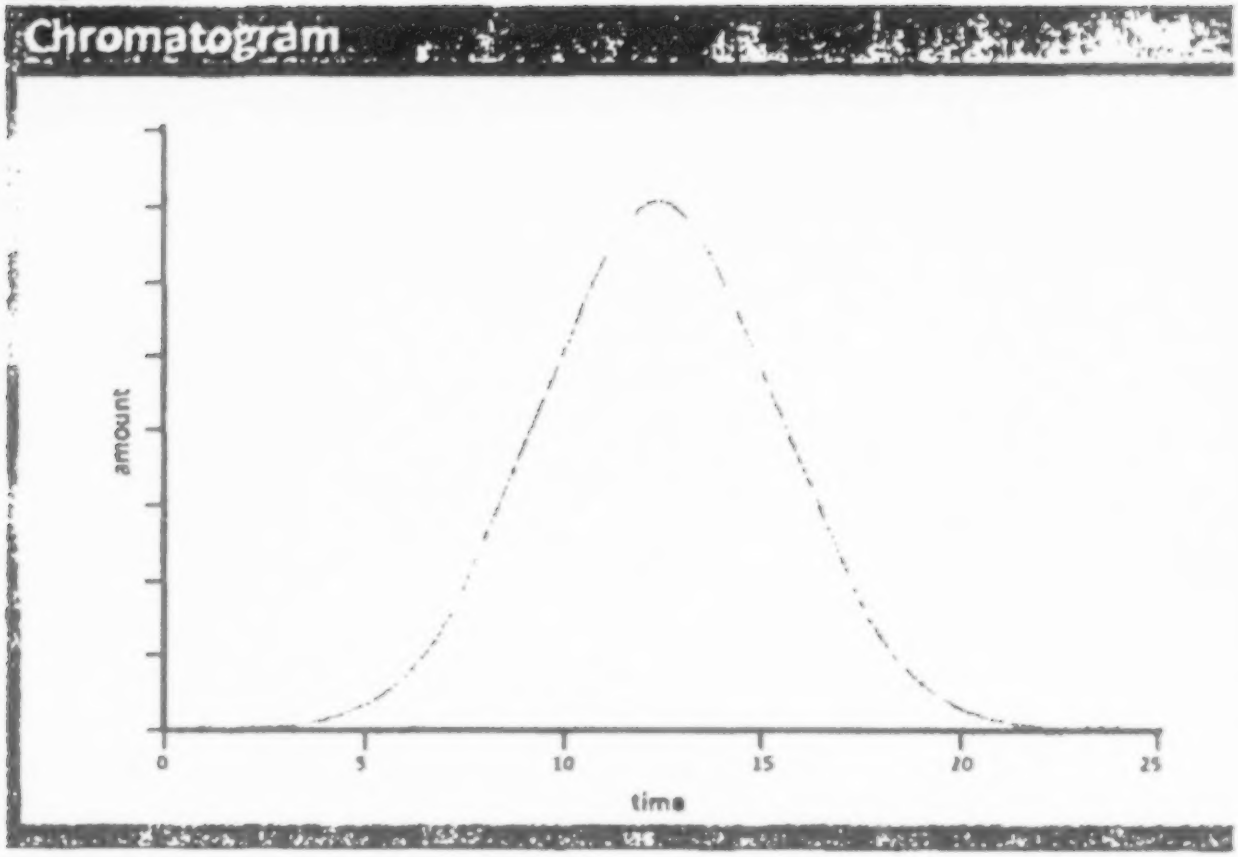
In 1994 (and to this day), SEC was the best method for determining the molecular weight distribution of a mixture of polypeptides like copolymer-1. Barth 1991, for example, describes SEC as "a well-recognized technique for the determination of polymer molecular weight distributions." (PTX 566 at 2.) Similarly, Billingham 1977 explains that SEC is "used as a matter of routine in very many polymer laboratories" to characterize the molecular weight of polydisperse polymers. (Sept. Tr. (Grant) 198:14-20, 329:14-20; PTX 514 at 200.)

SEC analysis utilizes a size exclusion (or gel filtration) column, which is a gel-filled glass or metal cylinder where the separation of molecules takes place. (Sept. Tr. (Grant) 198:4-8, 198:24-199:25; PTX 986 at 10-11.) The sample to be analyzed is introduced into the top of the column along with liquid which carries the sample down through the gel. (Sept. Tr. (Grant) 200:1-13; PTX 986 at 12-13.) The individual beads making up the separation gel have many pores of varying sizes. Size exclusion takes place because large molecules cannot get into the pores, and therefore pass through quickly, while smaller molecules can go into the pores to various extents, and they therefore travel a longer path through the column and come out later than the larger molecules. (Sept. Tr. (Grant) 199:12-25, 200:14-201:7; PTX 986 at 14-15.) For this reason, molecules of different sizes are separated from one another as they travel through the column.

The bottom of the column is connected through a tube to a detector. The detector detects the presence and the quantity (amount) of molecules exiting the

column. (Sept. Tr. (Grant) 201:8-24.) The output of the detector is a graph, called a chromatogram, which is plotted on the x-axis as time and on the y-axis as the amount of the material passing the detector at each point in time. (Sept. Tr. (Grant) 201:25-203:19; PTX 986 at 16; see Figure 1 below.) Larger molecules exit the column first due to the size exclusion. (Sept. Tr. (Grant) 200:23-201:7; PTX 986 at 13.) The highest point, or peak, of the chromatogram, represents the time at which the species of molecules present in the highest abundance passes by the detector. (Sept. Tr. (Grant) 1404:23-1405:9; PTX 969 (Svec Dep.) at 9:19-23; PTX 982.)

Figure 1



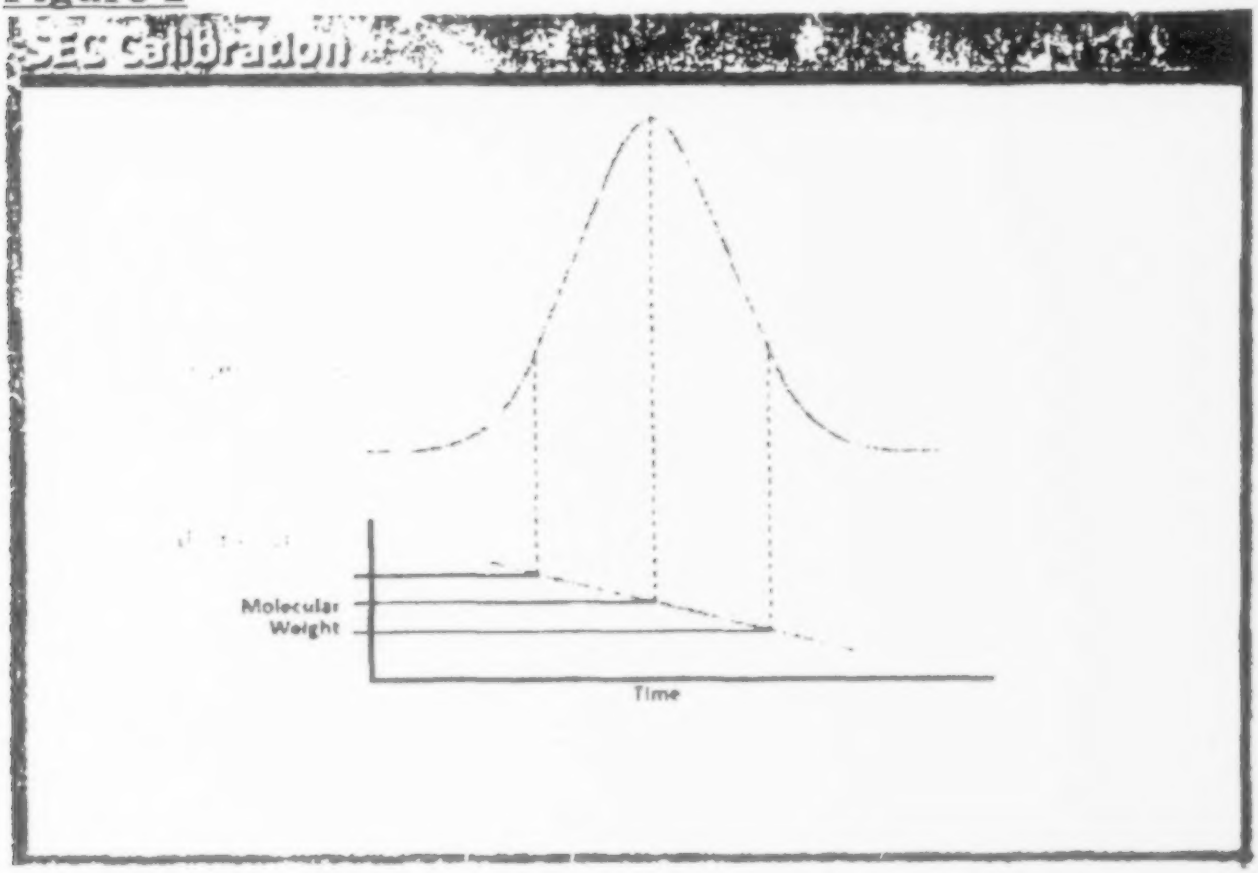
(PTX 986 at 16.)

To determine the molecular weight of the molecules exiting the column at each point (or time) along the chromatogram, it is necessary to have a calibration curve, which correlates the time at each point along the chromatogram's x-axis with the molecular weight of material exiting the column at that particular time. (Sept. Tr. (Grant) 203:20-204:3.) SEC calibration was well-understood in 1994. (Sept. Tr. (Grant) 204:4-5.) By that time, it was well-known that to create a calibration curve, calibration standards—molecules of known molecular weights—had to be run through the column to determine the time that they exited the SEC apparatus. The

molecular weight of each standard, which can be determined by a number of independent (non-SEC) methods, is plotted against the time at which the standard comes out of the column. (Sept. Tr. (Grant) 204:6-205:10; PTX 986 at 17.)

To determine the molecular weight at any point on the chromatogram—the peak, for example—one can match the time from the x-axis to the corresponding time on the calibration curve and read the molecular weight from the y-axis of the calibration curve. (Sept. Tr. (Grant) 205:11-206:2; PTX 986 at 18; see Figure 2 below.)

Figure 2



In 1994, it was known that there were at least two options for calibrating an SEC column to get accurate molecular weights for a polypeptide mixture like copolymer-1. The conventional way was to use calibration standards that have the same relationship between size and shape in solution (also known as "hydrodynamic volume")[8] and molecular weight as the sample being measured. The other alternative was to use "universal calibration." (Sept. Tr. (Grant) 206:3-208:20, 1399:18-1400:13; PTX 969 (Svec Dep.) at 94:21-95:5; PTX 990 at 2.)

With respect to the first method, the necessity of matching the hydrodynamic characteristics of the sample and the calibration standards in conventional SEC calibration was well-known to those skilled in the art and well-described in the literature in 1994. (Sept. Tr. (Grant) 1412:6-1413:16; Sept. Tr. (Scandella) 1314:15-1316:24; PTX 961 (Kota Dep.) at 18:3-14; PTX 962 (B. Rao Dep.) at 75:6-76:10, 78:14-80:5; PTX 973 (Venkataraman Dep.) at 108:20-109:23; PTX 974 (Wallingford Dep.) at 146:9-149:7; PTX 317 at MYL0000111; PTX 553 at 72.) For example, Janson 1989 states that "[t]he relationship between size and molecular weight of solutes is strongly dependent upon solute shape .... It is readily seen that calibration versus molecular weight is only meaningful for solutes of similar shape." (PTX 553 at 72.)

With respect to the second method, if standards that match the hydrodynamic volume to molecular

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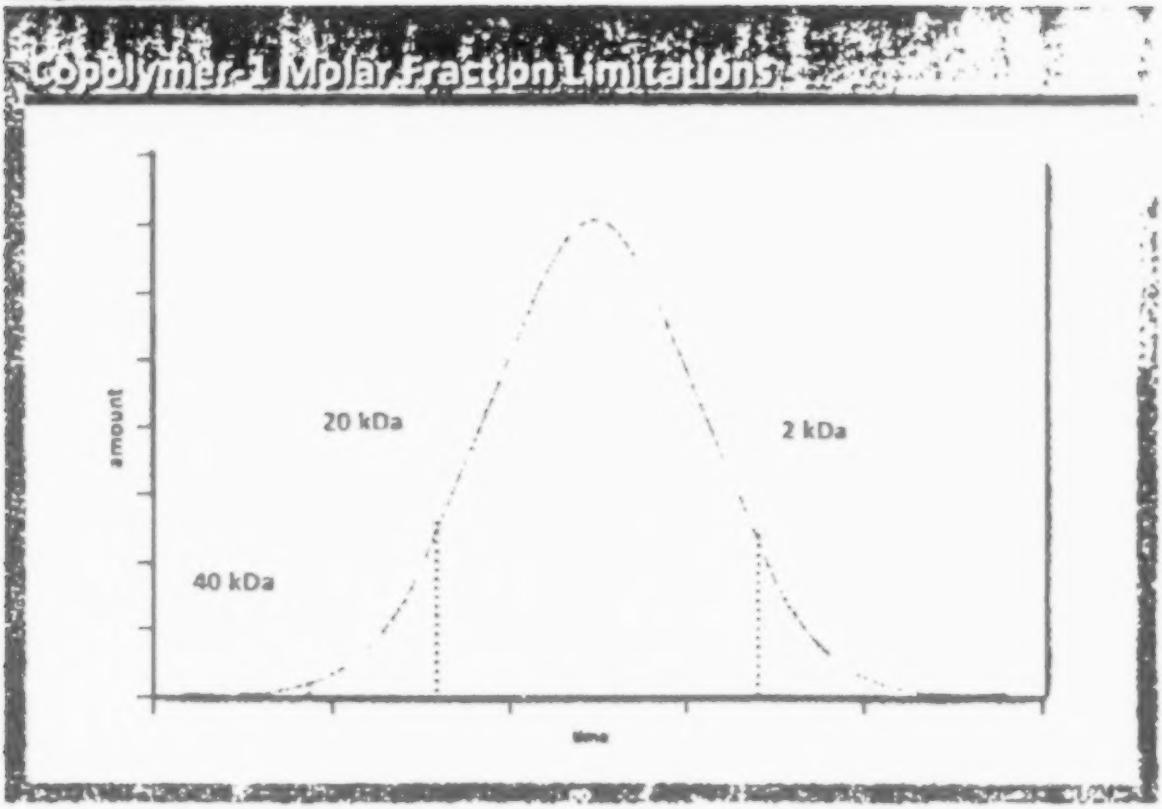
[8] At trial, this method was commonly referred to as "self-standards."

weight characteristics of the sample were unavailable, it was well-known that universal calibration could be used to determine an accurate molecular weight for a sample. (Sept. Tr. (Grant) 208:14-20, 1399:18-1400:13, 1401:12-18, 1413:17-23; PTX 970 (Svec Dep.) at 320:2-321:10, 326:14-327:10.) Universal calibration does not require the standards to have the same hydrodynamic volume to molecular weight relationship as the sample, because it uses a different physical property (intrinsic viscosity) to allow a correlation of the size of molecules exiting the column to their molecular weight. (Sept. Tr. (Grant) 208:14-20, 1400:6-15.)

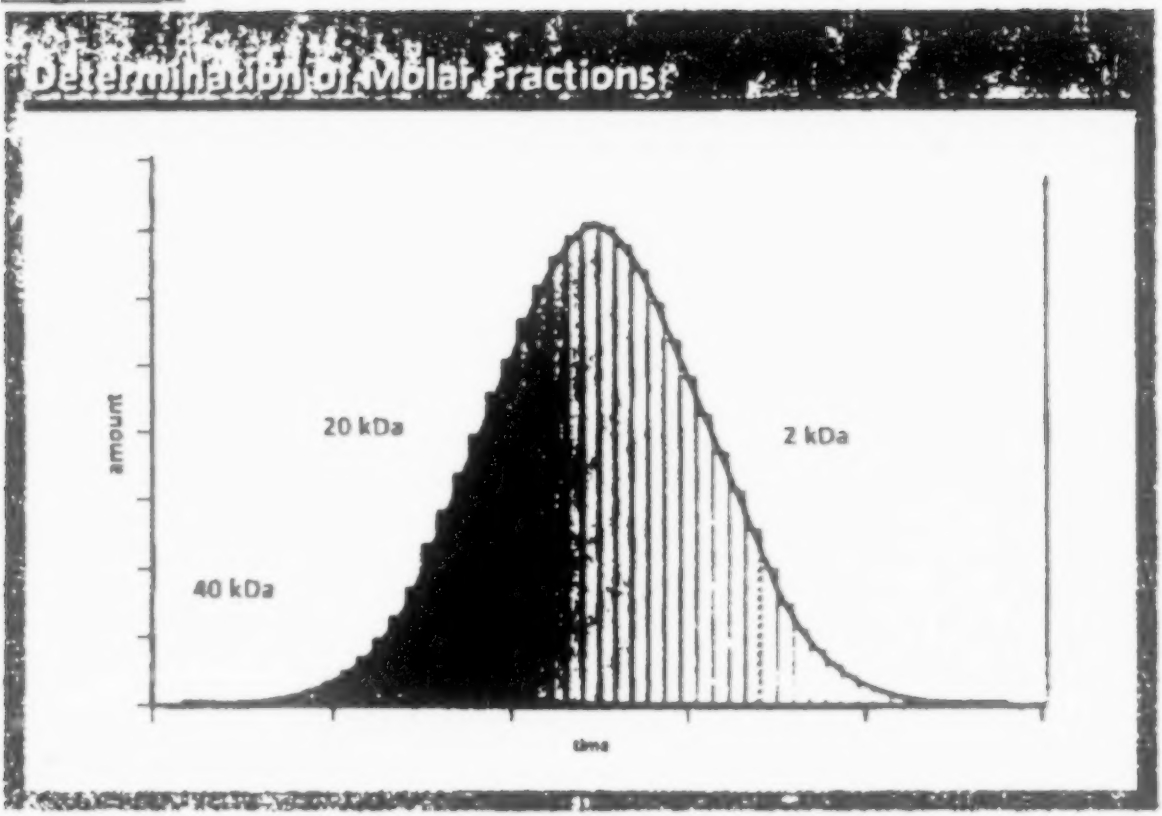
In addition to allowing determination of an average molecular weight, SEC allows the separation of molecules and the determination of the percentage of molecules having molecular weights falling within any given molecular weight range. (Sept. Tr. (Grant) 209:17-25, 227:8-22; PTX 986 at 33.) A chromatogram represents the amount of material that is exiting the size exclusion column at any particular time (as reflected on the x-axis). It also represents the entirety of the molecules in the sample. (Sept. Tr. (Grant) 203:14-19.) On the illustrative chromatogram shown below (Figure 3), the molecular weights of 40 kDa, 20 kDa, and 2 kDa are depicted from left to right because large molecules come out of the size exclusion column earlier than smaller molecules. (Sept. Tr. (Grant) 227:8-22; PTX 986 at 30.)

Figure 3



In order to calculate the percentage of species having a molecular weight within a certain range, the chromatogram is divided into slices, which can be represented by small rectangles, as shown in Figure 4 below. A molecular weight is assigned to each slice through the use of a calibration curve. The number of moles of the material, which represents the number of molecules in each slice, can be calculated by dividing the amount of the material in the slice by the molecular weight that has been assigned to that slice. (Sept. Tr. (Grant) 228:11-229:11, 230:8-12; PTX 986 at 31.)

Figure 4



The number of moles of all of the molecules falling within a molecular weight range—between 2 kDa and 20 kDa, for example —can be added together and divided by the total number of moles of all of the molecules present in the sample, as represented by the entire chromatogram. Multiplying this fraction by 100 gives the percentage (on a "molar fraction" basis) of molecules within the molecular weight range. Similarly, the molar percentage of molecules having molecular weights above 40 kDa can be calculated by dividing the number of moles of material having molecular weight above 40 kDa by the total number of moles of the materials represented by the entire chromatogram. (Sept. Tr. (Grant) 229:12-230:7; PTX 986 at 32.)

When using this method, it is not necessary to know how many different molecular weights are in each slice. It is acceptable to assign a single molecular weight to each slice. (Sept. Tr. (Grant) 298:11-299:3, 329:6-330:7; PTX 986 at 31.)

D. Level of Ordinary Skill in the Art

The level of ordinary skill in the art in this case is very high. Dr. Grant defined a person of ordinary skill in the art as having an "advanced degree or equivalent in a chemical or biological discipline and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides." The person of ordinary skill in the art would also have "access to and the ability to consult with other scientists having related and/or complementary knowledge and experience in the areas of polymer chemistry, biochemistry, analytical chemistry, separation technology, medicine, and toxicology." (Sept. Tr. (Grant) 189:19-190:6, 1398:11-17; PTX 986 at 3.)

Defendants' expert witnesses also defined the level of skill in the art as high. (Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9; Sept. Tr. (Wall) 1756:2-12; Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4.) Sandoz's expert, Dr. Scandella, for example, defined a person of ordinary skill in the art as having a Ph.D. in chemistry, biochemistry, or a related field with a minimum of three years of experience in chromatography, and specifically in SEC of macromolecules. (Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9.) Sandoz's other expert, Dr. Wall, defined a person of ordinary skill in the art as having

a Ph.D. in chemistry, biochemistry, or a related field, with three years of experience in chromatography or a person who has supervised or directed a research lab that conducts chromatography. (Sept. Tr. (Wall) 1756:2-12.)

Mylan's expert Dr. Zeiger defined a person of ordinary skill: "A person of ordinary skill in fields of biochemistry and immunology in 1994 would have had an advanced degree in a chemical or biological discipline, and extensive experience in the synthesis, fractionation, and characterization of polymers, such as their hydrodynamic and structural properties, as applied to proteins, synthetic peptides and/or polydisperse peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography (SEC), and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained." (Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4.) He also testified that he has "no problem" with Dr. Grant's definition of a person of ordinary skill in the art. (Sept. Tr. (Zeiger) 811:15.)

The Court accepts Dr. Grant's testimony and adopts his definition of the level of ordinary skill in the art.[9] In light of the nearly identical view of the

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[9] The Court accepts Dr. Grant's definition with the caveat, which is not part of Dr. Grant's quoted testimony above, that the relevant time period is May 24, 1994—the day the '037 application was filed. See PC Connector Solutions LLC v. SmartDisk Corp., 406 F.3d 1359, 1363 (Fed. Cir. 2005) (explaining, in context of claim construction, that a claim's

level of ordinary skill in the art put forward by the parties' experts, the Court notes that its analysis of the legal and factual issues is the same regardless of which expert's definition is used.

DISCUSSION

I. Infringement[10]

A. General Principles

A finding of patent infringement involves a two-step process. First, the claims must be construed.[11] Then, the construed claims must be compared to the accused products or processes to determine whether all of the limitations of at least one claim are present—literally or by a substantial equivalent. E.g., Acumed LLC v. Stryker Corp., 483 F.3d 800, 804 (Fed. Cir. 2007) (citations omitted). "To establish literal infringement, 'every limitation set forth in a claim must be found in an accused product, exactly.'" Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP, 616 F.3d 1249, 1253 (Fed. Cir. 2010) (citation omitted). "For process patent or method patent claims, infringement occurs when a party performs all of the steps of the process." BMC Res., Inc. v.

"meaning must be interpreted as of its effective filing date") (citations omitted).

[10] With respect to all claims and defenses, the Court separately states its findings of fact and conclusions of law pursuant to Rule 52(a) of the Federal Rules of Civil Procedure. Fed. R. Civ. P. 52(a).

[11] The Court issued its claim construction decision, construing the disputed claim terms, on August 29, 2011. (Dkt. 273 in 08 Civ. 7611; Dkt. 194 in 09 Civ. 8824.)

Paymentech, L.P., 498 F.3d 1373, 1379 (Fed. Cir. 2007) (citation omitted).

"'The doctrine of equivalents prevents an accused infringer from avoiding liability for infringement by changing only minor or insubstantial details of a claimed invention while retaining the invention's essential identity. The doctrine of equivalents is utilized '[t]o temper unsparing logic and prevent an infringer from stealing the benefit of the invention.' " Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd., 234 F.3d 558, 564 (Fed. Cir. 2000) (alteration in original) (citations and internal quotation marks omitted), vacated on other grounds by 535 U.S. 722 (2002). "Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art." Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1351 (Fed. Cir. 2003) (citations omitted). "[T]he insubstantial differences inquiry may be guided by determining whether the element in the accused device performs substantially the same function in substantially the same way to obtain the same result as the claim limitation." Id. (internal quotation marks omitted).

"'The patentee bears the burden of proving infringement by a preponderance of the evidence.'" Creative Compounds, LLC v. Starmark Labs., 651 F.3d 1303, 1314 (Fed. Cir. 2011) (citation omitted). The same preponderance of the evidence burden applies to patentees, such as Teva, asserting infringement under 35 U.S.C. § 271(e)(2). See

Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1365-66 (Fed. Cir. 2003). In Abbott Laboratories v. TorPharm, Inc., the Federal Circuit explained that "[a]n infringement inquiry provoked by an ANDA filing under 35 U.S.C. § 271(e)(2)(A) is focused on the product that is likely to be sold following FDA approval." 300 F.3d 1367, 1373 (Fed. Cir. 2002) (citation omitted); see also Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997) (explaining that "the question of infringement[,]" under 35 U.S.C. § 271(e) (2), "must focus on what the ANDA applicant will likely market if its application is approved"). "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." Abbott Labs., 300 F.3d at 1373 (citation omitted).

Lastly, pursuant to 35 U.S.C. § 271(b), " [w]hoever actively induces infringement of a patent shall be liable as an infringer." AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1056 (Fed. Cir. 2010). To establish induced infringement, a patentee must show by a preponderance of the evidence " 'the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement.' " AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1056 (Fed. Cir. 2010) (citation omitted).

B. Findings of Fact as to Mylan

i. Mylan's ANDA Product

The active ingredient in Mylan's proposed product is described as glatiramer acetate. (Sept. Tr. (Owens) 629:1-12; PTX 319 at MYL0000143; PTX 320 at MYL0000235-36; PTX 962 (B. Rao Dep. 06/09/2010) at 37:14-2; PTX 984 at 1.) Mylan's ANDA makes clear that glatiramer acetate was formerly known as, and is synonymous with, "copolymer-1." For example, copolymer-1 is listed in the Nomenclature section of the ANDA as a "synonym" for glatiramer acetate. (Sept. Tr. (Grant) 250:7-9; Sept. Tr. (Owens) 630:11-631:8; PTX 320 at MYL0000236.) The Manufacturing section of the ANDA refers to the product of Mylan's manufacturing process as "copolymer-1." (PTX 321 at MYL0000253, 622.) Mylan's proposed labeling also states that glatiramer acetate was "formerly known as copolymer-1." (Sept. Tr. (Gokel) 369:21-370:3; 372:14-18; 373:14-18; PTX 321 at MYL 0000253; PTX 734 at MYL0004956; PTX 962 (B. Rao Dep. 06/09/2010) at 192:6-10; PTX 987 at 55.)

Natco scientists also acknowledged that Mylan's proposed product is copolymer-1. Dr. Bhujanga Rao, Natco's President of Research & Development and 30(b)(6) witness, testified that the Mylan/Natco proposed product is a "copolymer-1 composition" and that Mylan's scientists understood that the terms "glatiramer acetate" and "copolymer-1" are "used interchangeably." (PTX 962 (B. Rao Dep. 06/09/2010) at 11:13-19, 23:20-24:2, 259:21-260:3.) Dr. Satyanarayana Kota, the general manager of Research & Development at Natco and the scientist

responsible for starting its peptide group, testified similarly that glatiramer acetate and copolymer-1 are "the same." (PTX 961 (Kota Dep.) at 28:1-16, 52:17-53:8, 202:15-25.)

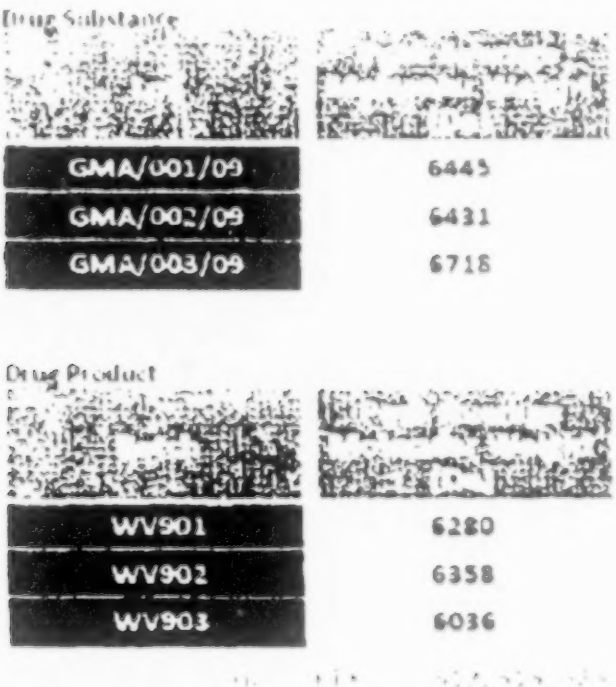
ii. Amino Acid Composition

The glatiramer acetate in Mylan's proposed product is composed of the following four amino acids: glutamic acid, alanine, lysine, and tyrosine. (Sept. Tr. (Gokel) 378:6-14; 394:17-395:2; PTX 320 at MYL0000237, 615-17.) Mylan's ANDA provides the molar fractions for these four amino acids, which represent the relative proportions of the four amino acids in Mylan's product. (Sept. Tr. (Gokel) 380:21-381:14, 394:17-395:22; PTX 325 at MYL0001050, 68, 79; PTX 961 (Kota Dep.) at 71:5-15, 111:25-112:16.) According to its ANDA, Mylan's glatiramer acetate lots have the following molar fractions of glutamic acid, alanine, tyrosine and lysine, respectively: Drug substance lot GMA/001/09, 0.144: 0.427: 0.092: 0.336; Drug substance lot GMA/002/09, 0.148: 0.432: 0.092: 0.328; Drug Substance lot GMA/003/09, 0.142: 0.440: 0.092: 0.327; Drug product lot WV901, 0.137: 0.462: 0.090: 0.311; Drug product lot WV902, 0.146: 0.463: 0.088: 0.3 04; and Drug product lot WV903, 0.144: 0.464: 0.088: 0.305. (Sept. Tr. (Gokel) 3 94:17-3 95:16, 399:20-400:1, 400:4-6; PTX 300 at MYL0002927; PTX 312 at MYL0002929; PTX 313 at MYL0002931; PTX 325 at MYL0001050, 68, 79; PTX 961 (Kota Dep.) at 111:25-112:16.)

iii. Molecular Weight

Mylan's specification for the peak average molecular weight of its proposed product is between 5,000 and 9,000 daltons. (Sept. Tr. (Grant) 249:21-251:20, 253:25-254:8, 312:1-22, 313:12-22, 314:21-315:3; PTX 300 at MYL0002928; PTX 312 at MYL0002930; PTX 313 at MYL0002932; PTX 318 at MYL00000107, 117; PTX 325 at MYL0001050, 68, 79; PTX 330 at MYL0000752, 765, 766; PTX 986 at 42, 43.) As set forth in Figure 5 below, the data in Mylan's ANDA demonstrates that each of its lots falls within the specified 5,000-9,000 daltons range. (Sept. Tr. (Grant) 249:17-251:20, 255:13-257:11, 257:18-258:3, 258:9-19, 258:25-259:23; PTX 300 at MYL0002928; PTX 312 at MYL0002930; PTX 313 at MYL0002932; PTX 318 at MYL00000107, 117; PTX 325 at MYL0001050, 1068, 179; PTX 986 at 42-44.)

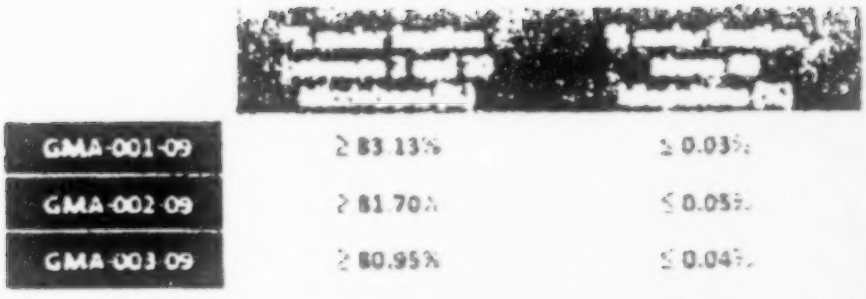
Figure 5



Mylan determined the peak molecular weight values in its ANDA using SEC with a Superose 12 column. (Sept. Tr. (Grant) 252:2-8, 254:12-20; PTX 323 at MYL0000765-66.) Mylan calibrated its SEC column using peptide standards that (i) had amino acid compositions consistent with the composition of copolymer-1 and (ii) had the same size-to-molecular weight relationship as copolymer-1. (Sept. Tr. (Grant) 250:23-251:7; PTX 323 at MYL0000765-66.) In addition to having a specified peak molecular weight, Mylan's proposed product also has particular molecular weight distribution characteristics, some of which are shown in Figure 6 below. (Sept. Tr. (Grant) 260:23-263:9; PTX 421; PTX 986 at 46.)

Dr. Grant used electronic molecular weight data generated by Mylan, during its SEC measurements of three Mylan drug substance lots, to calculate the percentage (on a molar fraction basis) of the copolymer-1 molecules in each lot having a molecular weight between 2 and 20 kilodaltons and the percentage having a molecular weight above 40 kilodaltons. (Sept. Tr. (Grant) 260:23-263:9; PTX 421; PTX 986 at 46.) Those percentages are listed in Figure 6 below:

Figure 6



GMA-001-09	≥ 83.13%	≤ 0.03%
GMA-002-09	≥ 81.70%	≤ 0.05%
GMA-003-09	≥ 80.95%	≤ 0.04%

Using the electronic molecular weight data for the same three Mylan drug substance lots, Dr. Grant also calculated the molar fraction percentage of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponds to each lot.[12] (Sept. Tr. (Grant)

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[12] Mylan criticized Dr. Grant's use of the electronic molecular weight data because it was generated using Mylan's original set of peptide standards as calibration markers. Mylan's critique is unfounded. Mylan argued that due to the limited number of standards, the calibration could not be extrapolated beyond the molecular weights of the peptide standards. But as Dr. Grant explained, Mylan's molecular weight software applied the calibration across the entire distribution. (Sept. Tr. (Grant) 318:17-321:5.) Moreover, using the same data, Mylan itself analyzed the molecular weight distribution of its proposed product and calculated the percentage of molecules having molecular weights between 2 and 20 kDa. Finally, Mylan calculated the weight average and number average molecular weights for its product. All of these calculations required Mylan to extrapolate its calibration beyond the molecular weights of the peptide standards to cover the entire molecular weight distribution. Demonstrating that extrapolation is appropriate, Mylan reported all of this information to the FDA based on its original set of peptide standards. (Sept. Tr. (Grant) 318:12-321:51; PTX 25 at 1057.)

263:22-265:9; PTX 421; PTX 986 at 50.) Those percentages are listed in Figure 7 below:

Figure 7

TFA copolymer-1 corresponding to sample	% TFA molar fraction between 2 and 20 kilodaltons
GMA-001-09	> 87.45
GMA-002-09	> 86.09
GMA-003-09	> 84.52

Source: PTX

During trial, Mylan produced to Teva additional electronic data for its proposed product generated using SEC with universal calibration. Using this newly-produced data, Dr. Grant performed another set of calculations of the molar fraction percentages for Mylan's lots. (Sept. Tr. (Grant) 1464:8-1468:4.) Consistent with his previous calculations, Dr. Grant found that, in each of Mylan's lots, greater than 90% of the copolymer-1 molecules on a molar fraction basis had molecular weights between 2 and 20 kilodaltons. (Sept. Tr. (Grant) 1465:16-25.) He also found that, in all lots, less than or equal to 2.5% by molar fraction of the copolymer-1 molecules had molecular weights above 40 kilodaltons. (Sept. Tr. (Grant) 1466:9-19.)

Dr. Grant also calculated the molar fraction percentage of molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponds to each of Mylan's lots based on the universal calibration data produced

during trial. (Sept. Tr. (Grant) 1466:1-19.) He found the percentage to be greater than or equal to 90% for all lots. (Sept. Tr. (Grant) 1466:1-8.)

iv. Mylan's Manufacturing Process

Natco scientist Dr. Kota was part of the team responsible for developing Natco's proposed generic product. (PTX 962 (Rao Dep. 06/09/2010) at 26:8-27:4, 35:4-8; PTX 963 (Rao Dep. 09/30/2010) at 27:20-28:23.) When he began working on the project, he consulted the scientific literature regarding copolymer-1, including at least some of the patents-in-suit. (PTX 961 (Kota Dep.) at 31:7-14, 31:24-32:16, 40:15-42:22, 42:24-51:19; PTX 962 (Rao Dep. 06/09/2010) at 26:8-27:4; PTX 963 (B. Rao Dep. 09/30/2010) at 19:11-21:22.) [redacted] Sept. Tr. (Gokel) 374:14-375:5; PTX 270 at NAT0121552; PTX 961 (Kota Dep.) at 80:6-82:8, 82:23-84:25, 85:2-3.)

[redacted] (PTX 270 at NAT0121552; PTX 728 at NAT0028763; PTX 961 (Kota Dep.) at 77:18-23, 77:25-78:7, 80:6-82:8, 82:23-84:25, 85:2-3, 191:16-192:22, 194:18-195:21, 197:22-200:16.) [redacted] (PTX 728 at NAT0028763; PTX 961 (Kota Dep.) at 197:22-200:16.) [redacted]

[redacted] (PTX 961 at 78:1-7.)

[redacted] (PTX 192; PTX 961 (Kota Dep.) at 184:15-185:14; PTX 962 (B. Rao 06/09/2010 Dep.) at 165:20-166:16, 168:5-11; 168:14-169:15.) [redacted]

[redacted] (PTX 1 at 6:5-12; PTX 728 at NAT0028763; PTX 961 (Kota Dep.) at 200:17-201:12, 202:15-203:5, 203:16-25.) [redacted] (PTX 270 at NAT0121552; PTX 961 (Kota Dep.) at 80:6-82:8, 82:23-84:25, 85:2-3), [redacted] (PTX 963 (B. Rao 09/30/2010 Dep.) at 42:11-44:7, 44:9-45:12, 45:14-46:15, 46:17-25.)

v. ANDA Process

Section 3.2.S.2 of Mylan's ANDA, entitled "Manufacture," sets forth the manufacturing process for Mylan's proposed glatiramer acetate product. (PTX 321.) Although Mylan has filed amendments to its ANDA, it has not revised its manufacturing process or produced any new exhibit batches since its original ANDA filing.

Mylan uses the same four-step process to make its glatiramer acetate active ingredient set forth in the patents-in-suit (the "patent process"), which is described above. In Step 1 of the Mylan ANDA process, like in Step 1 of the patent process, the N-carboxyanhydrides of the amino acids alanine, glutamic acid, lysine, and tyrosine are combined with the initiator diethylamine to form long chains. (Sept. Tr. (Gokel) 348:13-22, 370:7-371:17; PTX 321 at MYL0000251, MYL0000260.) Like the patent process, the glutamic acids and lysines used in Step 1 of the Mylan process must have benzyl and TFA protecting groups, respectively. (Sept. Tr. (Gokel) 342:16-343:23, 345:5-346:10; PTX 987 at 12-13.) Step 1 results in a mixture of polypeptide chains that are referred to in Mylan's ANDA as GMA Fl or protected copolymer-1. (Sept. Tr. (Gokel) 371:18-21; PTX 321 at MYL0000251, MYL0000254; PTX 987 at 47-52.) Protected copolymer-1 still has the benzyl protecting groups on the glutamic acids and the TFA protecting groups on the lysines. (Sept. Tr. (Gokel) 371:18-372:18; PTX 321 at MYL0000251.)

In Step 2 of Mylan's process, as in the patent process, protected copolymer-1 is reacted with HBr/acetic acid. (Sept. Tr. (Gokel) 371:22-372:6; PTX 321 at MYL0000252; PTX 987 at 53-54.) Like in the patent process, the addition of HBr/acetic acid serves two purposes. First, it removes the benzyl protecting groups from the glutamic acids. Second, it cleaves, or cuts, the polypeptide chains. (Sept. Tr. (Gokel) 371:22-372:6; Sept. Tr. (Sampson) 1641:8-17; PTX 987 at 16-18.) The process of cleaving the polypeptide chains is known as depolymerization. (Sept. Tr. (Gokel) 349:11-18; PTX 987 at 16-18, 53-54.) The

product of Mylan's Step 2 reaction is TFA-copolymer-1. (Sept. Tr. (Gokel) 371:22-372:18; PTX 987 at 53.)

As in the patent process, Step 2 is used to control the molecular weight of Mylan's product so that it meets the specification of 5,000 to 9,000 daltons. (Sept. Tr. (Gokel) 349:12-350:10, 3 71:22-372:6, 444:13-447:5; Sept. Tr. (Sampson) 1641:8-1642:8; PTX 321 at MYL0000645-51.) In order to determine the time and temperature at which to run Step 2 so that the final copolymer-1 product has the targeted average molecular weight of between 5,000 and 9,000 daltons, Mylan ran a series of test reactions. (Sept. Tr. (Gokel) 445:4-447:11; PTX 321 at MYL0000645-49; PTX 961 (Kota Dep.) at 124:4-127:11.)

[redacted]

Mylan applied these time and temperature determinations, based on the test reactions, to its ANDA process. (Sept. Tr. (Gokel) 447:2-6; PTX 320 at MYL0000272-73; PTX 321 at MYL0000647, MYL0000649; PTX 964 at 120:23-122:9, 125:10-126:20.) [redacted]

[redacted]

In Step 3 of Mylan's process, TFA-copolymer-1 is treated with piperidine, which removes the TFA protecting groups from the lysines. (Sept. Tr. (Gokel) 372:14-18; PTX 321 at MYL0000253; PTX 987 at 55.) The patent process also employs this step.

In Step 4 of Mylan's process, as in the patent process, the resulting product from Step 3 is purified

by diafiltration using acetic acid. (Sept. Tr. (Gokel) 372:14-23, 373:8-17; PTX 321 at MYL0000253, 267.) The product of Step 4 is glatiramer acetate, or copolymer-1. (Sept. Tr. (Gokel) 372:14-18, 373:3-5; PTX 321 at MYL0000621; PTX 987 at 55.)

vi. Mylan's ANDA Product Label

The proposed label for Mylan's proposed product has the same indication and dosage information as Teva's label for Copaxone®. (Sept. Tr. (Lisak) at 141:13-145:6; PTX 697; PTX 734 at MYL0004949.) Mylan's proposed product label states that the product is "indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis." (Sept. Tr. (Lisak) at 141:13-145:6; PTX 734 at MYL0004949.) If Mylan's product is approved by the FDA, its use would comprise a method of treating multiple sclerosis (Sept. Tr. (Lisak) at 145:21-146:1; 146:23-147:1), and Mylan's proposed label would encourage physicians to use the ANDA product to treat patients with multiple sclerosis (Sept. Tr. (Lisak) 147:16-19; PTX 963 (B. Rao 09/30/2010 Dep.) at 226:17-22; PTX 971 (Talton Dep.) at 85 :17-21.)

C. Conclusions of Law as to Mylan's Product

i. Mylan's Proposed Product Infringes Each of the Asserted Claims because Mylan's Product is Copolymer-1

The Court construed "copolymer-1" to mean "a mixture of polypeptides composed of alanine,

glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively, non-uniform with respect to molecular weight and sequence, which is synthesized by polymerization of suitably protected amino acid carboxyanhydrides." (CCO at 12.) Mylan does not contest that its product is a "mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine;" that it is "non-uniform with respect to molecular weight and sequence;" and is "synthesized by polymerization of suitably protected amino acid carboxyanhydrides." Moreover, the evidence at trial established that Mylan's proposed product, in fact, meets those limitations. (Sept. Tr. (Grant) 250:7-12; Sept. Tr. (Gokel) 377:5-378:10; 413:22-415:9.)

Mylan nevertheless argues its product is not copolymer-1 because the molar ratio of the amino acids in its product is not approximately 6:2:5:1. The evidence at trial was to the contrary, however. It showed that Mylan's proposed product has a molar ratio of approximately 6:2:5:1 and, thus, is copolymer-1 within the meaning of the claims of the patents-in-suit.

A "molar ratio" is a means of expressing the relative proportions of each of the components in a mixture. (Sept. Tr. (Gokel) 378:20-379:11.) The molar ratio of "approximately 6:2:5:1" describes the relative proportions of the four amino acids alanine, glutamic acid, lysine, and tyrosine in copolymer-1. (Sept. Tr. (Gokel) 411:21-412:1.) For every 14 amino acids, approximately 6 will be alanine, approximately 2 will be glutamic acid, approximately 5 will be lysine, and approximately 1 will be tyrosine. (Sept. Tr. (Gokel)

381:6-14; PTX 987 at 67.) Because the sum of 6 + 2 + 5 + 1 is 14, the molar ratio 6:2:5:1 is expressed on a scale of 14. (Sept. Tr. (Gokel) 411:24-412:1.)

As shown below in Figure 8, the molar ratio of 6:2:5:1 can be expressed in different ways:

Figure 8

Molar Ratio of 6:2:5:1 Expressed in Different Ways

Amino Acid	Ratio	Fraction	Percent
	6	$^{6}/_{14}$ = .43	43%
	2	$^{2}/_{14}$ = .14	14%
	5	$^{5}/_{14}$ = .36	36%
	1	$^{1}/_{14}$ = .07	7%
Scale	14	1	100%

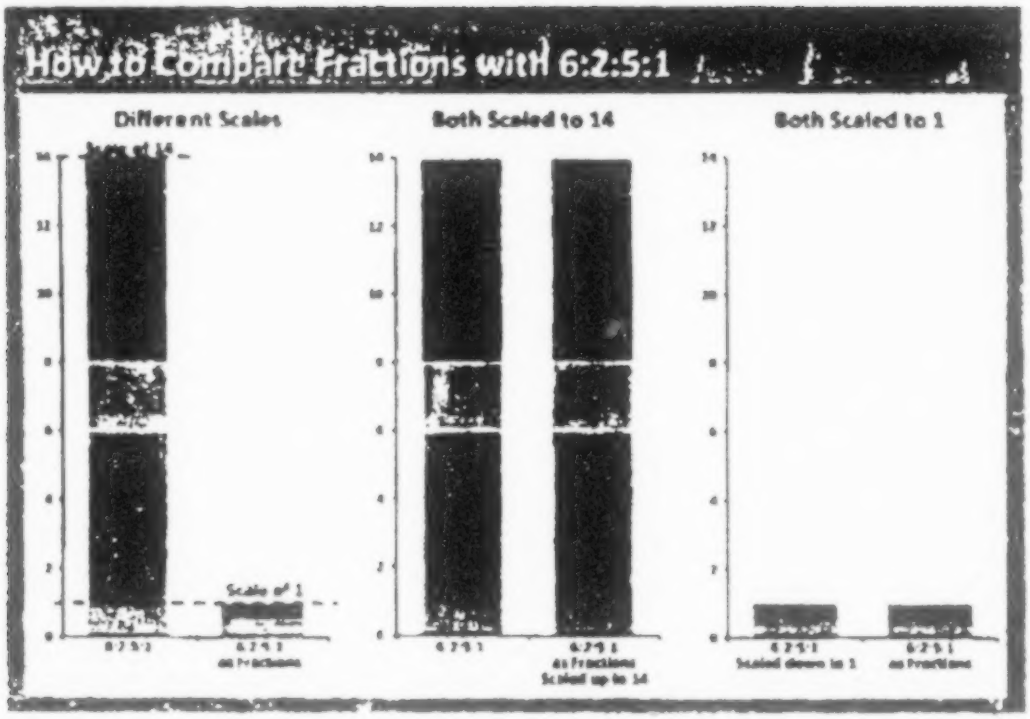
(PTX 987 at 67.) For example, approximately 6:2:5:1 can be expressed as the percentages of the four amino acids in a copolymer-1 mixture, which, by definition, must add up to 100%: approximately 6 out of 14, or approximately 43%, are alanine; approximately 2 out of 14, or approximately 14%, are glutamic acid; approximately 5 out of 14, or approximately 36%, are lysine; and approximately 1 out of 14, or approximately 7%, are tyrosine. (Sept. Tr. (Gokel) 381:24-382:3; PTX 987 at 67.)

The molar ratio of approximately 6:2:5:1 can also be expressed in terms of molar fractions, which, by definition, must add up to 1. Expressed in this manner, the molar fraction of alanine would be approximately 0.43; the molar fraction of glutamic acid would be approximately 0.14; the molar fraction of lysine would be approximately 0.36; and the molar fraction of tyrosine would be approximately 0.07. (Sept. Tr. (Gokel) 381:6-14; PTX 987 at 67.)

Whether expressed as (1) "approximately 6:2:5:1;" (2) approximately 43% alanine, 14% glutamic acid, 36% lysine, and 7% tyrosine; or (3) approximate molar fractions of 0.43 alanine, 0.14 glutamic acid, 0.36 lysine, and 0.07 tyrosine, the molar fractions all represent the same copolymer-1 compositions with the same relative proportions of the same four amino acids. (Sept. Tr. (Gokel) 381:6-382:15; PTX 987 at 67.)

To determine whether a sample has a molar ratio of "approximately 6:2:5:1," one can compare the sample using the 6:2:5:1 scale of 14, the percentages of the amino acids scale of 100%, or the molar fraction scale of 1. For the comparison to be accurate, the amino acid composition of the sample and 6:2:5:1 must be expressed on the same scale. (Sept. Tr. (Gokel) 382:23-383:15.). Failure to put the two on the same scale will give skewed and fallacious results, as demonstrated below in Figure 9.

Figure 9



(PTX 987 at 70.)

In its ANDA, Mylan provides the molar ratios for its proposed product in terms of molar fractions. (Sept. Tr. (Owens 629:19-21; Sept. Tr. (Gokel) 394:17-396:21, 399:20-400:1, 400:4-6; Sept. Tr. (Owens) 629:19-21; PTX 300 at MYL0002927; PTX 312 at MYL0002929; PTX 313 at MYL0002931; PTX 325 at MYL0001050; PTX 961 (Kota Dep.) at 111:25-112:16; PTX 987 at 74, 77, 78.) To determine whether Mylan's product meets the "approximately 6:2:5:1" limitation, "6:2:5:1" can be converted to molar fractions and then compared directly to the molar fractions in Mylan's ANDA. Alternatively, Mylan's molar fraction data can be converted to a scale of 14 and then compared directly to 6:2:5:1. (Sept. Tr. (Gokel) 395:17-387:25; PTX 987 at 74-75.) The crucial thing, again, is that the comparison be

performed on the same scale. The data for Mylan's Drug Substance Lot GMA/001/009 are compared both ways in Figure 10 below: Figure 10

Figure 10

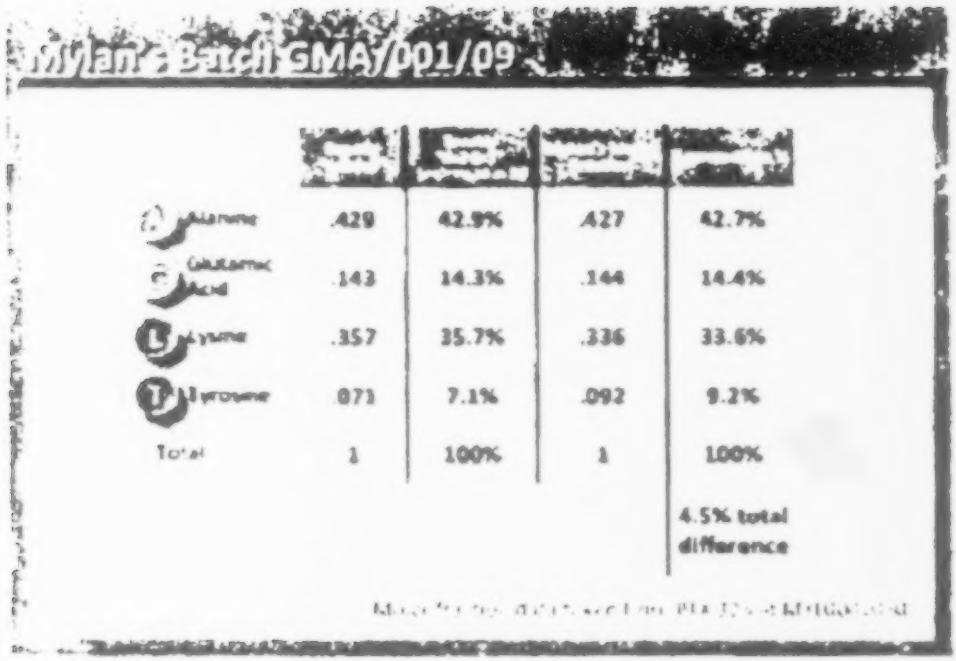
Mylan Drug Substance Lot GMA/001/09

Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot GMA/001/09 (Scale = 1)	Scale = 14		
A	6	.43	.427	x 14	5.98	6
B	2	.14	.144	x 14	2.02	2
E	5	.36	.336	x 14	4.70	5
T	1	.07	.092	x 14	1.29	1
Scale	14	1	1		14	14

(Sept. Tr. (Gokel) 396:3-397:9; PTX 987 at 74.)

Mylan's molar fraction data and 6:2:5:1 could also be converted to percentages and then compared directly. That comparison is shown in Figure 11 below:

Figure 11



(Sept. Tr. (Sampson) 543:1-544:17; PTX 988 at 2.)

As shown above, copolymer-1 with a molar ratio of exactly 6:2:5:1 would have 42.9% alanine, 14.3% glutamic acid, 35.7% lysine, and 7.1% tyrosine. Using the molar fractions reported for GMA/001/09 in Mylan's ANDA, the percentages of each amino acid in the batch are 42.7% alanine, 14.4% glutamic acid, 33.6% lysine, and 9.2% tyrosine. (PTX 988 at 2; Sept. Trial (Sampson) 543:22-545:4; PTX 988 at 2.) The percent differences in alanine, glutamic acid, lysine and tyrosine are therefore 0.2, 0.1, 2.1, and 2.1 percentage points, respectively, resulting in a total difference of 4.5% between the molar ratio of Mylan's product and exactly 6:2:5:1. (Sept. Trial (Sampson) 543:14-545:4; PTX 988 at 2.)

At trial, Mylan's expert, Dr. Kent, testified that the difference in the molar fraction of tyrosine between

Mylan's product and a product with a molar ratio of exactly 6:2:5:1 is 30%. (E.g., Sept. Trial (Kent) 715:3-9.) This is incorrect. Although there is a 30% difference, as a matter of arithmetic, between the numbers.071 (molar fraction of tyrosine in a product of exactly 6:2:5:1) and.092 (molar fraction of tyrosine in Mylan's product), that does not mean that the molar ratios differ by 30%. Dr. Sampson explained that in order to properly compare the molar fractions, one has to look at the compositions of the two copolymers in their entirety and not simply focus on a single amino acid. Looking at the compositions as a whole, there is a 2.1% difference in the tyrosine content, since one batch has 7.1% and the other has 9.2%. (Sept. Tr. (Sampson) 545:23-546:20.)

To determine whether the 4.5% total molar ratio difference between Mylan's product and exactly 6:2:5:1 falls within the scope of "approximately"—including the 2.1% difference in tyrosine content—the Court looks to the specification of the patents-in-suit and the prosecution history. See Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1056 (Fed. Cir. 1988) ("We note that the height and position limitation in the claim are modified by the terms 'substantially' and 'approximately.' These terms must be interpreted in light of the specification and prosecution history to determine the literal coverage of the claims with respect to height and position.").

Turning to the specification first, the person of ordinary-skill in the art would understand that the molar ratio of 6:2:5:1 is reported in one significant figure. In plain terms, this means that the molar ratio is reported as 6:2:5:1 as opposed to 6.0: 2.0: 5.0:

1.0, for example. Because 6, 2, 5, and 1 are whole numbers and not precise, a person of ordinary-skill in the art would understand that each of these numbers—6, 2, 5, and 1—encompasses its rounding range. (Sept. Tr. (Gokel) 384 :4-385 : 8.)

The person of ordinary skill in the art would also understand that the specification of the patents-in-suit cites to Teitelbaum 1971 in connection with the description of copolymer-1. One of ordinary skill would, thus, look to that article in order to gain an understanding of the scope of "approximately 6:2:5:1." (PTX 1 at 23-26; Sept. Tr. (Gokel) 387:25-389:8; PTX 499.) Table 1 of Teitelbaum 1971 is entitled "Composition of copolymer 1." It provides, among other things, the molar ratios for two batches that are expressly defined as "copolymer-1." Copolymer-1 Batch 1 is reported as having a molar ratio for alanine, glutamic acid, lysine, and tyrosine of 6.0: 1.9: 4.7: 1.0, respectively. Copolymer-1 Batch 2 is reported as having a molar ratio for alanine, glutamic acid, lysine, and tyrosine of 6.7: 2.1: 4.2: 1.0, respectively. (Sept. Tr. (Gokel) 390:16-25; Sept. Tr. (Sampson) 550:18-551:2; PTX 499 at 243; Sept. Tr. (Kent) 726:16-24.)

The authors of the article report that they considered the amino acid compositions of the two batches to be the same. (PTX 499 at 247; Sept. Tr. (Sampson) 552:12-18.) The total percent difference between the molar ratio of Teitelbaum 1971 Batch 2 and the molar ratio of exactly 6:2:5:1 is 12%. One of ordinary skill in the art would understand that the scope of "approximately 6:2:5:1" must be broad enough to include the molar ratio of Teitelbaum 1971

Batch 2, which was expressly defined as copolymer-1. Accordingly, the scope of "approximately 6:2:5:1" must, at a minimum, include total amino acid content differences of up to 12% from exactly 6:2:5:1. (Sept. Tr. (Gokel) 391:1-392:15; Sept. Tr. (Sampson) 551:3-21; PTX 987 at 71; PTX 499 at 243; PTX 988 at 5.)

The prosecution history of the "539 patent also provides guidance on the scope of "approximately 6:2:5:1." In a December 1, 2004 submission to the PTO during the prosecution of the '539 patent, Teva amended the claims to recite "copolymer-1" and explained to the PTO the meaning of that term as used in the claims. (PTX 20-A at TEV000304802.) Teva told the PTO that "the term "copolymer-1' is not limited to a specific molar ratio of amino acids." Teva explained that "[t]he molar ratio of the polypeptides of 1 copolymer-1' varies slightly based on the particular batch and the particular analytical methodology used." Teva pointed, as an example, to the two batches of copolymer-1 in Teitelbaum 1971 discussed above. (PTX 20-A at TEV000304802; Sept. Tr. (Kent) 736:17-737:10; PTX 20-A at TEV000304802.)

Teva also directed the PTO to three batches of copolymer-1 used in the Bornstein trial that had molar ratios of "1.9: 4.0: 6.0: 1.0," "1.8: 3.9: 5.7: 1.0," and "1.9: 4.0: 6.3: 1.0." (PTX 20-A at TEV000304802; Sept. Trial. Tr. (Kent) 737:11-22.) These molar ratios, rearranged and expressed as ratios of alanine to glutamic acid to lysine to tyrosine, are 6.0: 1.9: 4.0: 1.0, 5.7: 1.8: 3.9: 1.0, and 6.3: 1.9: 4.0: 1.0.

Based on the prosecution history, the term "approximately 6:2:5:1" must be broad enough to include the molar ratios of the Teitelbaum 1971 batches, as well as the three Bornstein batches —all of which were expressly defined as copolymer-1. See Monsanto Co. v. Bayer BioScience N.V., 363 F.3d 1235, 1244-45 (Fed. Cir. 2004) (finding improper the limitation of claims to a particular class of plants where the specification and prosecution history contained express statements that applicants had not limited claims in such a manner). Since the amino acid molar ratio of Mylan's proposed product differs from exactly "6:2:5:1" by only 4.5%, it is closer to exactly 6:2:5:1 than both the amino acid molar ratios of Teitelbaum Batch 2 and the Bornstein batches referred to during the prosecution history. The Court thus finds that Mylan's product falls within the scope of "approximately 6:2:5:1."

Mylan's argument for why its product does not meet the "approximately 6:2:5:1" limitation, and therefore is not copolymer-1, rests in large part on the testimony of its expert Dr. Kent. In Dr. Kent's opinion, in order to determine whether Mylan's copolymer-1 meets the "approximately 6:2:5:1" requirement, the molar fractions for each of the four amino acids provided in Mylan's ANDA must first be divided by the molar fraction for tyrosine. (Sept. Tr. (Kent) 701:6-23.) This mathematical procedure is referred to as "normalizing" to tyrosine. (Sept. Tr. (Gokel) 400:21-401:20; Sept. Tr. (Kent) 712:1-8.) The resulting values for glutamic acid, lysine, alanine and tyrosine must then be compared directly to 6, 2, 5, and 1, respectively. (Sept. Tr. (Kent) 701:6-702:13.) If the value of any single amino acid differs by more

than 10%, according to Dr. Kent, the composition cannot be copolymer-1. (Sept. Tr. (Kent) 703:5-704:8.) In regard to how he arrived at 10%, at trial, Dr. Kent testified that, in 1994, a person of ordinary skill in the art would expect to obtain reproducible amino acid results with less than 5% uncertainty and that the "common cutoff" for comparing samples is two standard deviations—10%. (Sept. Tr. (Kent) 703:5-704:5.)

Dr. Kent's opinion about the meaning and scope of approximately 6:2:5:1 is wrong for several reasons. First, Dr. Kent's opinion on the scope of "approximately 6:2:5:1" would exclude from the definition of copolymer-1 batches that the inventors themselves identified as copolymer-1 and batches that Teva expressly represented to the PTO were copolymer-1. See Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 909 (Fed. Cir. 2004) (district court erred in construing claim term narrowly where prosecution history showed that patentee intended a broader scope).

Specifically, Dr. Kent testified that using his definition of "approximately 6:2:5:1," Teitelbaum 1971 Batch 2 is not copolymer-1 despite the fact that the inventors themselves defined it as copolymer-1. (Sept. Tr. (Kent) 726:16-24, 728:18-24.) Dr. Kent attempted to explain away this flaw in his opinion by asserting that the molar ratio of Batch 2 never appeared in the literature after Teitelbaum 1971. As he was forced to eventually concede, however, the molar ratio of Batch 2 was reported in at least two later publications. (Sept. Tr. (Kent) 731:4-22; PTX 508 at 280; Sept. Tr. (Kent) 732:6-733:4; PTX 976 at

285.) Dr. Kent testified similarly that the three Bornstein batches that Teva expressly identified as copolymer-1 during the prosecution of the "539 patent were also not copolymer-1 using his definition of "approximately 6:2:5:1." (Sept. Tr. (Kent) 741:3-18.) The Court rejects this opinion because it is "squarely contrary" to the prosecution history. See Liebel-Flarsheim Co., 358 F.3d at 909.

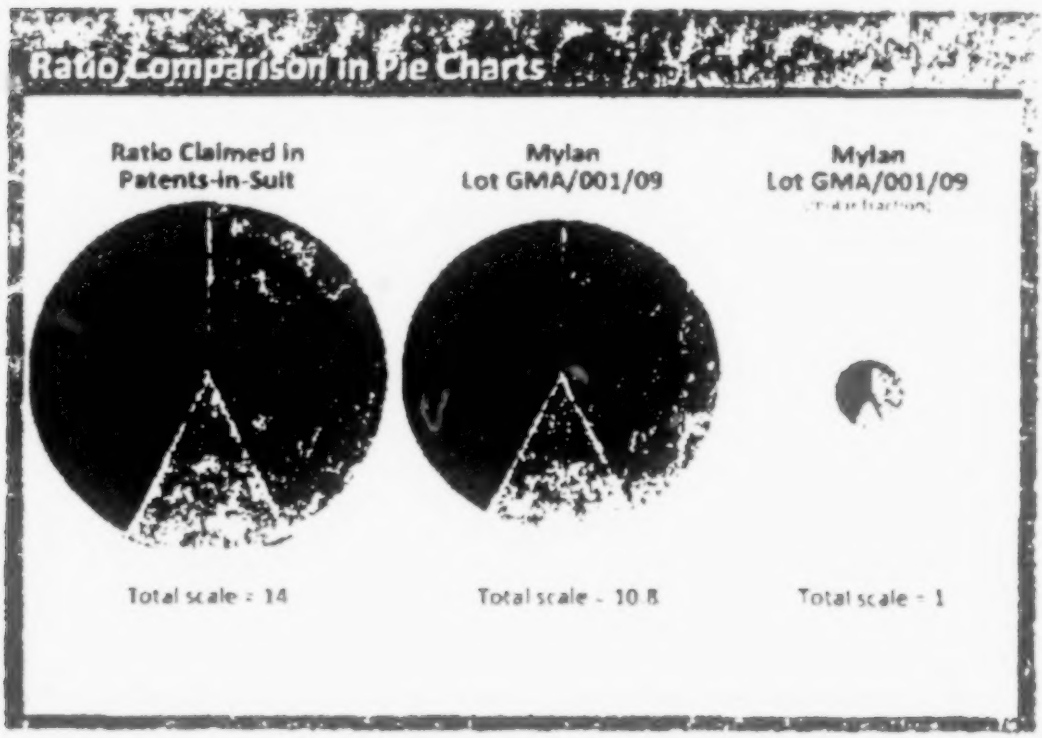
Second, nothing requires that Mylan's molar fraction data be normalized to tyrosine before comparing it to 6:2:5:1, as Dr. Kent suggests. The patents-in-suit make no mention of normalizing to tyrosine. (Sept. Tr. (Kent) 749:3-6.) And despite testifying that it is common practice to normalize to the least abundant species, Dr. Kent conceded he does not do so in his own work outside the context of this litigation. (Sept. Tr. (Kent) 747:22-748:16.)

Significantly, Dr. Kent admitted, during cross-examination, that the best way to compare the amino acid compositions of samples is by comparing their molar fractions, not their molar ratios. (Sept. Tr. (Kent) 743:10-15; 744:1-13.) Dr. Kent also acknowledged that either molar ratios or molar fractions could be used to determine whether a sample has a molar ratio of approximately 6:2:5:1. (Sept. Tr. (Kent) 743:16-21.)

Moreover, as explained above, the molar ratio of Mylan's product cannot be directly compared to 6:2:5:1 unless both numbers are on the same scale. (Sept. Tr. (Gokel) 382:23-383:15, 401:21-402:9; PTX 987 at 68.) As set forth above, "approximately 6:2:5:1" is expressed on a scale of 14. Mylan's molar

ratio data in its ANDA is expressed as molar fractions on a scale of 1. Normalizing this molar fraction data to tyrosine, as Dr. Kent requires, converts Mylan's molar ratio to a scale of 10.8. As shown in Figure 12 below, this puts the numbers on different scales and leads to an invalid comparison. (Sept. Tr. (Gokel) 400:21-402:9, 411:14-412:19; Sept. Tr. (Sampson) 555:24-556 :11; PTX 987 at 79.)

Figure 12



Third, in regard to Dr. Kent's 10% "common cutoff" (Sept. Tr. (Kent) 703:15-704:5), Dr. Kent offered nothing to support this opinion. Dr. Gokel, by contrast, whom the Court credits, testified that the level of uncertainty in amino acid analysis, as of 1994, was in the range of 10-20%, and supported his opinion by pointing to Crabb et. al., "A Collaborative Amino Acid Analysis Study From The Association of

Biomolecular Resource Facilities," Current Research in Protein Chemistry, 49-61 (1990) ("Crabb 1990"). As Dr. Gokel testified, Crabb 1990 reports that the precision of amino acid analysis varied from 11.4% to 26.4%. (Sept. Tr. (Gokel) 385:16-386:20; PTX 558 at 54-55.)

Dr. Gokel explained that the molar ratio "approximately 6:2:5:1" cannot be more precise than the experiments used to determine the molar fractions of each amino acid. (Sept. Tr. (Gokel) 386:21-25.) Thus, the scope of "approximately 6:2:5:1" would have to include, at a minimum, the 10-20% uncertainty in amino acid analysis. Using Dr. Kent's formula of two standard deviations, this would translate to a 20-40% "cutoff" when comparing samples to exactly 6:2:5:1.

Thus, even if Dr. Kent were correct that the term "approximately" should include only those samples within two standard deviations of exactly 6:2:5:1, that would include samples in which any of the amino acids differed by as much as 20-40% from exactly 6:2:5:1.

Finally, Dr. Kent testified that a copolymer-1 molar ratio of approximately 6:2:5:1 requires the presence of a bromotyrosine impurity. (Sept. Tr. (Kent) 756:9-757:18.) Following this view to its logical end, pure copolymer-1 with no impurities would not fall within the Court's construction of copolymer-1. Indeed, Dr. Kent testified that if a person of ordinary skill in the art followed the exact procedure for making copolymer-1 described in the patents-in-suit and used high quality HBr with no

free bromine in it, the resulting product would not be copolymer-1. (Sept. Tr. (Kent) 758:10-24.) This cannot be the case.

ii. The Reason for Mylan's Molar Ratio is Irrelevant to the Infringement Analysis.

The crux of Mylan's non-infringement argument is that its manufacturing process is different from the one set forth in the patents-in-suit. This difference, according to Mylan, affects the molar ratios of copolymer-1. The reason Mylan's product has a particular molar ratio is irrelevant, however, to the infringement analysis. The only question with respect to infringement is whether Mylan's product has a molar ratio of "approximately 6:2:5:1" and therefore is copolymer-1 within the meaning of the claims. See Acumed LLC, 483 F.3d at 804 ("A finding of patent infringement requires a two-step process: first, the court determines the meaning of the disputed claim terms, then the accused device is compared to the claims as construed to determine infringement.") (citation omitted).

Even if Mylan's argument were relevant, which it is not, it is contrary to the evidence. According to Mylan, making copolymer-1 pursuant to the process described in the patents-in- suit leads to an undisclosed side reaction. This side reaction occurs during the first deprotection step, in which the HBr/acetic acid solution is used to remove the benzyl protecting groups from the glutamic acid residues. The undisclosed side reaction results in the

formation of a fifth amino acid—bromotyrosine. (Sept. Tr. (Kent) at 657:9-658:6.)

As Dr. Kent acknowledged at trial, however, this side reaction does not necessarily occur when practicing the process in the patents-in-suit:

> Q. If you had HBr that was very pure and didn't contain any free bromine, then you wouldn't have bromotyrosine formation, right?
>
> A. That's correct.
>
> Q. So one way of controlling the formation of bromotyrosine would be to use high quality HBr that didn't have free bromine, right.
>
> A. Yes, that's absolutely correct.

(Sept. Tr. (Kent) at 754:3-10.) Thus, in 1994, a person of ordinary skill in the art could have followed the process for making copolymer-1 found in the patents-in-suit without forming any bromotyrosine. (Sept. Tr. (Kent) 754:3-10, 755:16-22.)

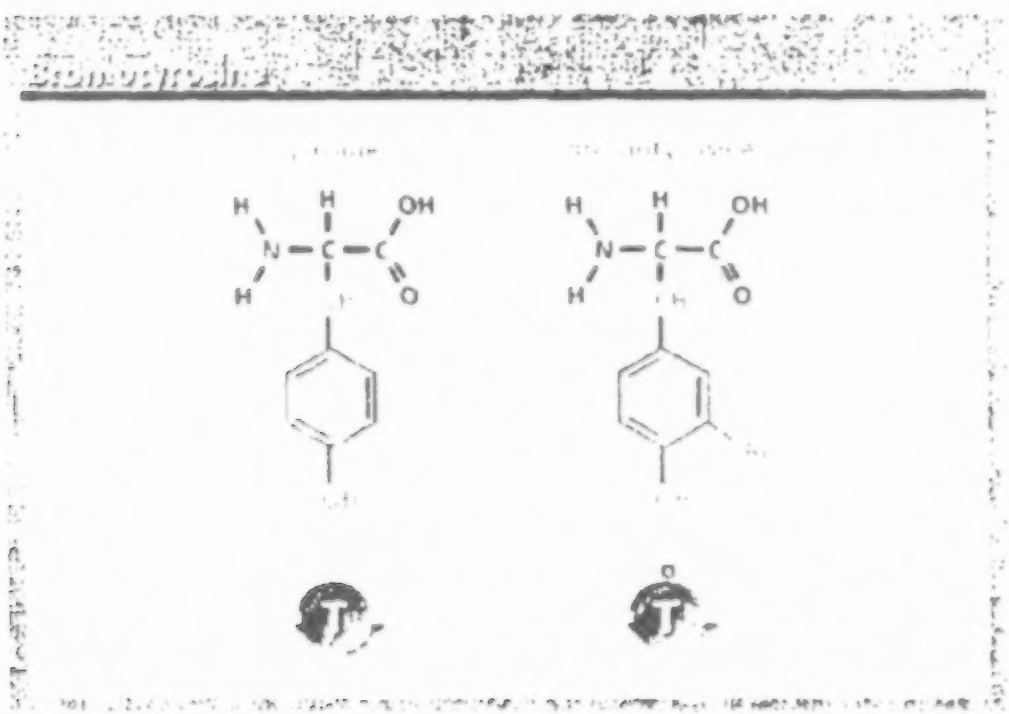
Mylan's argument that its product, made with phenol, has about 30% more tyrosine than a copolymer-1 composition made without phenol is also belied by the evidence. At trial, Mylan's Vice-President of Global Research and Development, acknowledged that at least some of Mylan's copolymer-1 batches made using phenol had a lower tyrosine content than batches made without phenol. (Sept. Tr. (Owens) at 639:6-8.)

The Court also finds that Mylan's characterization of bromotyrosine as a "fifth amino acid" in copolymer-1 is misleading. As an initial matter, tyrosine and bromotyrosine are not two unrelated molecules. Referring to Figure 13 below, Dr. Kent conceded the similarities between the two:

> Q. Okay. In any event, bromotyrosine is the tyrosine molecule exactly the same except one position on the molecule has a bromine added, correct?
>
> A. It is exactly the same. If you take the compound on the left and replace one proton with a bromine on the aromatic ring, then you have bromotyrosine, that's correct.

(Sept. Tr. (Kent) 759:15-20.)

Figure 13



(PTX 989 at 6.)

The Court notes that outside the context of this litigation, Mylan does not refer to bromotyrosine as a "fifth amino acid" in copolymer-1. In its ANDA, Mylan represented to the FDA that there are four—not five—amino acids in copolymer-1: alanine, glutamic acid, lysine, and tyrosine. The ANDA discusses the presence of bromotyrosine, but only as an impurity. It is never referred to as a possible fifth amino acid in the copolymer-1 composition.[13] (Sept. Tr. (Kent) 771:24-772:3; Sept. Tr. (Owens) 632:4-6, 632:11-633:6; Sept. Tr. (Gokel) 1597:24-1598:2; PTX 320 at MYL0000685-86.)

Finally, if the impurity bromotyrosine were to be considered a "fifth amino acid" in copolymer-1, then there would also be "sixth" and "seventh" amino acids—the impurities benzyl glutamic acid and TFA-lysine. (Sept. Tr. (Gokel) 1597:24-1600:23; Sept. Tr. (Kent) 772:11-25; PTX 987 at 4, 13.) Mylan has made no such claim.[14]

iii. The Doctrine of Equivalents

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[13] Sandoz also represented to the FDA that bromotyrosine may be an impurity in copolymer-1. It likewise never referred to bromotyrosine as a possible "fifth amino acid" in the copolymer-1 composition. (Sept. Tr. (Gokel) 1603:13-1606:16; PTX 349 at SDZ00017963, SDZ00018149.)

[14] To the extent Mylan argues that Copaxone® does not have a molar ratio of 6:2:5:1 because it is manufactured using phenol, the Court need not consider this argument. The molar ratio of Copaxone® is not the issue here. The issue is whether Mylan's proposed product infringes the patents-in-suit.

Even if Mylan's proposed product did not literally meet the requirement of a molar ratio of "approximately 6:2:5:1," it infringes under the doctrine of equivalents. See Boehringer Ingelheim Vetmedica, Inc., 320 F.3d at 1351 ("Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are "insubstantial' to one of ordinary skill in the art.") (citations omitted).

At trial, Dr. Sampson testified that the difference between the molar ratio of Mylan's proposed product and "approximately 6:2:5:1" is insubstantial and, therefore, is equivalent to "approximately 6:2:5:1." (Sept. Tr. (Sampson) 543:14-545:4, 552:24-553:15; 557:20-23.) In support of her opinion, Dr. Sampson pointed to, among other things, the data in Teitelbaum 1971. As explained above, Table 1 of Teitelbaum 1971 shows the molar ratios for two batches of copolymer-1. The molar ratio of alanine, glutamic acid, lysine, and tyrosine for Batch 1 is 6.0: 1.9: 4.7: and the molar ratio for Batch 2 is 6.7: 2.1: 4. . (PTX 499; Sept. Tr. (Sampson) 550:18-551:2.) There is a 2% total difference between the molar ratio of Batch 1 and exactly 6:2:5:1 and a 12% total difference between the molar ratio of Batch 2 and exactly 6:2:5:1. (PTX 988 at 5; Sept. Tr. (Sampson) 552:3-21.) Despite these differences in molar ratio, the two batches were reported as being equally effective in suppressing EAE. (Sept. Tr. (Sampson) 549:11-24; PTX 499 at 247 (Table 8).) In fact, the authors themselves concluded that the two batches of copolymer-1 showed similar biological

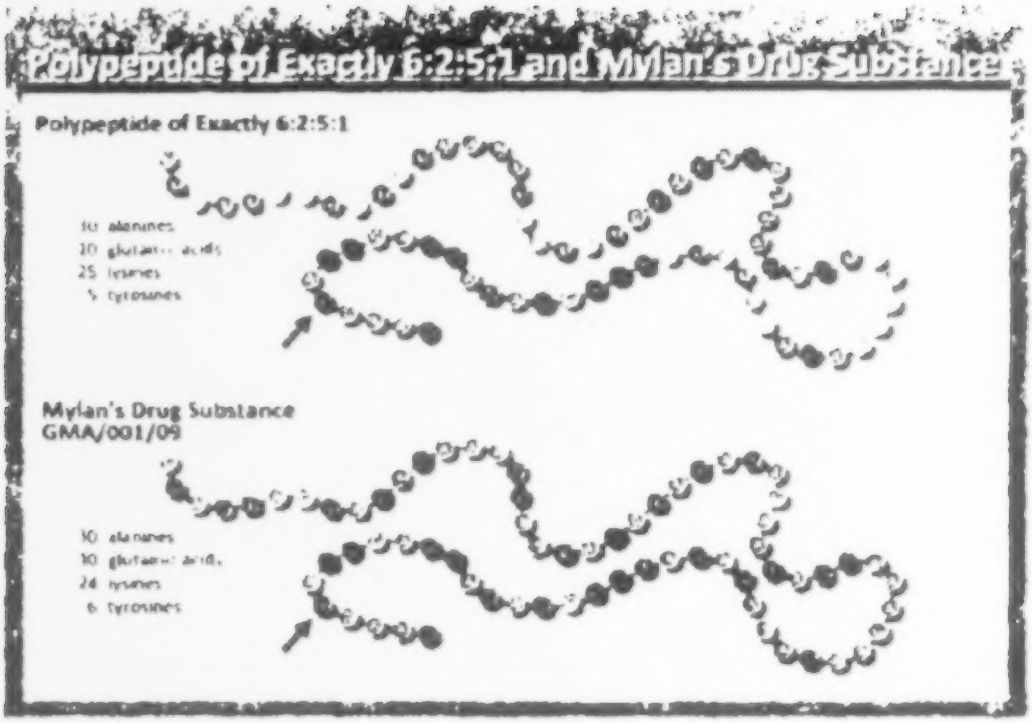
activity. (PTX 499 at 247; Sept. Tr. (Sampson) 552:12-18.)

Thus, as Dr. Sampson testified, Teitelbaum 1971 demonstrates that a total amino acid difference of up to 12% from exactly 6:2:5:1 does not materially affect the biological activity of a copolymer-1 sample. Mylan's drug substance, which differs from exactly "6:2:5:1" by only 4.5%, would therefore not be expected to have materially different biological activity from a copolymer-1 sample with a molar ratio of exactly 6:2:5:1. (Sept. Tr. (Sampson) 552:14-553:15.) Indeed, Mylan's testing of its own product demonstrates that it is biologically active in the EAE model. (PTX 318; Sept. Tr. (Owens) 640:23-641:17.)

Accordingly, the molar ratio of Mylan's proposed product is insubstantially different from "approximately "6:2:5:1." (Sept. Tr. (Sampson) 543:14-544:17, 552:14-553:15.) See Boehringer Ingelheim Vetmedica, Inc., 320 F.3d at 1351 (relying on similar biological properties to conclude that claimed and accused elements were insubstantially different and, therefore, equivalent).

Dr. Sampson also explained that the 4.5% total difference between the molar ratio of the amino acids in Mylan's proposed product and exactly 6:2:5:1 translates into a single amino acid difference for an average copolymer-1 chain with 70 amino acids, which would have a molecular weight of about 7,500 daltons. (Sept. Tr. (Sampson) 548:1-18.) This single amino acid difference is illustrated in Figure 14 below.

Figure 14



(PTX 987 at 81; PTX 988 at 4.)

By contrast, as can be seen in Figure 15 below, there is a four amino acid difference in that same 70 amino acid chain between Batch 2 of Teitelbaum 1971 and a polypeptide having a molar ratio of exactly "6:2:5:1." (Sept. Tr. (Sampson) 556:12-557 :19.)

Figure 15

(PTX 988 at 10.)

The single amino acid difference in Mylan's product cannot be viewed as substantial in light of the four amino acid difference of Teitelbaum Batch 2, which is expressly defined as copolymer-1.

In their proposed findings of fact and conclusions of law, Mylan argues, for the first time, that prosecution history estoppel and the prohibition against recapturing subject matter deliberately left unclaimed bars Teva from expanding the scope of "approximately 6:2:5:1" under the doctrine of equivalents. According to Mylan, during the prosecution of the "098 patent, Teva surrendered any equivalents of copolymer-1 having a molar ratio of "approximately 6:2:5:1."

It is well-settled "that a party's failure to include a legal theory or defense in the pre-trial order results in its subsequent abandonment or waiver." Colli v. Wirth, No. 94 Civ. 3234 (LBS), 1996 WL 442835, at *1 (S.D.N.Y. Aug. 6, 1996) (citations omitted). The reason for this rule is simple: to prevent "trial by ambush." See, e.g., Katt v. City of New York, 151 F. Supp. 2d 313, 347 (S.D.N.Y. 2001). Mylan's prosecution history estoppel argument is even more egregious than "trial by ambush" because it waited until after the trial to raise this defense. See Id.

Had Mylan raised this defense earlier, Teva could have attempted to "overcome the presumption that prosecution history estoppel bars a finding of equivalence"—assuming Mylan had been able to establish the defense—by providing "expert testimony and ... other extrinsic evidence relating to the relevant factual inquiries[,]" including, "for example, the state of the art and the understanding of a hypothetical person of ordinary skill in the art at the time of the amendment." See Glaxo Wellcome, Inc. v. Impax Labs., Inc., 356 F.3d 1348, 1353-54 (Fed. Cir. 2004) (citations and internal quotation marks omitted). Without notice that it needed to provide any evidence to this effect, Teva was clearly prejudiced by Mylan's failure to raise this defense until after the conclusion of the trial. Accordingly, the Court finds that Mylan waived its prosecution history estoppel argument with regard to infringement under the doctrine of equivalents. See, e.g., Colli, 1996 WL 442835, at *1-2.

For the reasons set forth above, even if the molar ratio of the amino acids in Mylan's product did not

fall within the literal scope of "approximately 6:2:5:1," which it does, it would be equivalent to "approximately 6:2:5:1."

iv. Mylan's Product Meets the Molecular Weight Limitations

The molecular weight limitations of the asserted claims can be divided into three categories: 1) average molecular weight limitations; 2) copolymer-1 fraction limitations; and 3) TFA copolymer-1 fraction limitations. At trial, Dr. Grant explained why Mylan's ANDA product meets the molecular weight limitations of each of the asserted claims. (Sept. Tr. (Grant) 265:2-268:3.) Mylan offered no evidence rebutting Dr. Grant's conclusions.

1) Average Molecular Weight Limitations

The Court construed "average molecular weight" to mean "peak molecular weight detected using an appropriately calibrated suitable gel filtration column." (CCO at 40 and n.10; Sept. Tr. (Grant) 211:5-15; PTX 986 at 25.) Mylan's method for determining the peak molecular weight values of its product involves using an appropriately calibrated suitable gel filtration column. (Sept. Tr. (Grant) 250:23-254:22; PTX 318 at MYL0000111-12; PTX 330 at MYL0000765-66.)

Based on Dr. Grant's testimony, which the Court credits, and the peak molecular weight data in Mylan's /ANDA, Mylan's proposed product meets the molecular weight limitations of claim 1 of the "808

patent and claim 1 of the "589 patent, which require a copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons;" claims 1 and 6 of the x847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the "539 patent, which require a copolymer-1 having an average molecular weight of "about 4 to about 9 kilodaltons;" and claim 10 of the "539 patent, which requires a copolymer-1 with an average molecular weight of "6.25 to 8.4 kilodaltons." (Sept. Tr. (Grant) 259:24-260:22; PTX 986 at 24, 45.)

2) Copolymer-1 Molar Fraction Limitations

Based on Dr. Grant's calculations using Mylan's electronic data, which the Court credits, Mylan's proposed product meets the molecular weight limitations of Claims 1, 2, and 3 of the "430 patent, which require the copolymer-1 to have over 75% of its molar fraction within the molecular weight range of 2 and 20 kDa; claims 8 and 3 0 of the v53 9 patent, which require the copolymer-1 to have less than 2.5% of its molar fraction with molecular weights above 40 kDa; claims 9, 10, and 31 of the "539 patent and claim 8 of the "098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 2.5% of its molar fraction with molecular weights greater than 40 kDa; claim 1 of the 476 patent, claim 1 of the "161 patent, and claim 1 of the "098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 5% of its molar fraction with molecular weights greater than

40 kDa. (Sept. Tr. (Grant) 262:14-263:21; 1463:16-1465:25; 1466:9-19.)

3) TFA Copolymer-1 Molar Fraction Limitations

Based on Dr. Grant's calculations using Mylan's electronic data, which the Court credits, Mylan's proposed product meets the molecular weight limitations of Claims 1, 2, and 3 of the M30 patent, claim 1 of the v476 patent, and claim 1 of the "161 patent, which require that the TFA copolymer-1 that is made as a result of treatment of protected copolymer-1 with hydrobromic acid have over 75% of its molar fraction with molecular weights between 2 and 20 kDa. (Sept. Tr. (Grant) 265:2-15.)

v. Mylan's Process Meets the Process Limitations

Of the 22 asserted claims of the patents-in-suit, twelve claims are directed either to a method of manufacturing copolymer-1 or to a copolymer-1 that is made by a particular process. Mylan has not disputed that the manufacturing process in its ANDA meets these claim limitations.

Based on the information in Mylan's ANDA, the stipulation entered into by Mylan, and Dr. Gokel's testimony, Mylan's process meets the "reacting protected copolymer-1 with hydrobromic acid" limitation found in claim 1 of the "808 patent, claim 1 of the "589 patent, claims 1, 2, and 3 of the "898 patent, claims 1, 2, and 3 of the "430 patent, claim 1 of the "476 patent, and claim 1 of the "161 patent;

the "treating trifluoroacetyl copolymer-1" limitation found in claim 1 of the "808 patent, claim 1 of the "589 patent, claims 1, 2, and 3 of the "898 patent, claims 1, 2, and 3 of the "430 patent, claim 1 of the "476 patent, claim 1 of the "161 patent, and claims 1 and 6 of the "847 patent; the "purifying" limitation found in claim 1 of the "808 patent, claim 1 of the "589 patent, and claims 1 and 6 of the "847 patent; the "selecting a predetermined molecular weight profile" limitation of claims 1, 2, and 3 of the "898 patent; the "for a time and at a temperature predetermined by test reaction" limitations of claims 1, 2, and 3 of the "898 patent, claims 1, 2, and 3 of the "430 patent, claim 1 of the "476 patent, and claim 1 of the "161 patent; and the "copolymer-1 fraction" limitations of claim 1 of the "161 patent and claim 1 of the "476 patent. (Sept. Tr. (In Chambers Stip.) 440-43; Sept. Tr. (Gokel) 349:4-350:18, 368:14-374:9, 439:11-447:19; 447:12-17, 448:16-469:7; 478:10-469:7; PTX 321 at MYL0000251-54, 262, 647, 649; PTX 987 at 45-55, 100-10.)

vi. Mylan Meets the Treatment Limitations

At trial, Dr. Lisak testified regarding Mylan's infringement of the claim limitations related to treatment of multiple sclerosis. His testimony was unrebuttted. Based on his testimony, which the Court credits, Mylan's proposed product meets the "method of treating multiple sclerosis" limitation found in claim 1 of the '476 patent; the "administering to a subject in need thereof" limitation found in claim 1 of the '476 patent; the "pharmaceutically effective amount" limitation found

in claim 1 of the v476 patent and claim 1 of the '161 patent; the "treatment of multiple sclerosis" limitation found in claim 1 of the '161 patent; the "suitable for treating multiple sclerosis" limitation found in claim 1 of the "539 patent; the "dose therapeutically effective to treat multiple sclerosis" limitation found in claim 12 of the '539 patent; the "a method for treating a patient suffering from multiple sclerosis" limitation found in claims 23, 30, and 31 of the '539 patent; the "administering to a patient in need thereof" limitation found in claims 23, 30, and 31 of the '539 patent; and the "suitable for treating multiple sclerosis" limitation found in claim 1 of the "098 patent. (Sept. Tr. (Lisak) 137:5-147:19; PTX 734 at MYL0004949; PTX 985 at 20.)

In addition, based on the stipulation entered into by Mylan, Mylan's proposed product meets the limitations of "pharmaceutical composition" and "pharmaceutically acceptable excipient" in claims 12, 23, 30, and 31 of the "539 patent. (PTX 935.)

Finally, the Court finds that Mylan would induce physicians to infringe the "476 and "539 patents if its ANDA were approved. Mylan knew of those patents before filing its ANDA, as it filed a certification with the FDA and sent a notice letter to Teva specifically referencing the patents-in-suit, including the "476 patent and the "539 patent. (PTX 965 (S. Rao Dep.) at 123:25-124:14; JPO ¶¶ 89-90, 94-95.) Mylan's proposed product label would induce doctors to prescribe its ANDA product to treat multiple sclerosis and thereby induce infringement of claim 1 of the "476 patent and claims 23, 30, and 31 of the "539 patent. See AstraZeneca LP, 633 F.3d at 1060

("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the alleged infringer's] affirmative intent to induce infringement.") (citation omitted).

vii. Mylan Infringes All Asserted Claims

In sum, based on the testimony of Dr. Lisak, Dr. Grant, Dr. Sampson, and Dr. Gokel, the evidence they discussed and referenced during their testimony, and Mylan's stipulations, the Court finds, by a preponderance of the evidence, that the manufacture and sale of Mylan's proposed glatiramer acetate product would infringe each of the asserted claims both literally and under the doctrine of equivalents.

D. Findings of Fact as to Sandoz

i. Sandoz's ANDA Product and its Active Ingredient

The active ingredient in Sandoz's proposed product is described as glatiramer acetate. (Sept. Tr. (Gokel) 360:16-18.) Sandoz and Momenta acknowledge that glatiramer acetate is also known as copolymer-1. For example, Sandoz's labeling for its proposed product describes its active ingredient as "glatiramer acetate (formerly known as copolymer-1)." (Sept. Tr. (Lisak) 141:13-143:19; PTX 206 at SDZ00000031.) Sandoz internal documents likewise make clear that one of the names for its active ingredient is "copolymer-1." (Sept. Tr. (Grant) 220:13-221:7; PTX 141 at

MMT00391607.) In addition, Momenta scientist Mani Iyer, who was in charge of manufacturing and developing Sandoz's glatiramer acetate, specifically testified that Sandoz's product is a "copolymer-1 composition." (PTX 960 (Iyer Dep.) at 25:8-10.)

1) Amino Acid Composition

The glatiramer acetate active ingredient in Sandoz's proposed product is composed of the four amino acids glutamic acid, alanine, lysine and tyrosine. (Sept. Tr. (Gokel) 414:23-415:9; PTX 219 at SDZ00002024-25; PTX 351 at SDZ00018614.) Sandoz's ANDA provides data on the relative proportions of glutamic acid, alanine, lysine and tyrosine in its proposed product, expressed as molar fractions. (Sept. Tr. (Gokel) 417:19-22, 420:12-17; PTX 219 at SDZ00002025; PTX 913 at 28.) According to Sandoz's ANDA, the lots it produced have the following molar fractions of glutamic acid, alanine, tyrosine and lysine, respectively: drug substance lots 077K7277, 0.147: 0.436: 0.083: 0.334; drug substance lot 087K7253, 0.142: 0.419: 0.083: 0.356; drug product lot CT0743, 0.134: 0.444: 0.083: 0.340; and drug product lot CT0750, 0.126: 0.421: 0.083: 0.370. (Sept. Tr. (Gokel) 416:14-419:6; PTX 219 at SDZ00002025; PTX 987 at 89.)

In its [redacted] Briefing Book, Sandoz provided the molar fractions for an additional drug substance lot—lot 051M7282. (Sept. Tr. (Gokel) 420:3-17.) The molar fractions of glutamic acid, alanine, tyrosine, and lysine for this lot are 0.136: 0.427: 0.093: 0.344. (Sept. Tr. (Gokel) 420:3-17; Sept. Tr. (Sampson)

546:22-547:15; PTX 913 at 28; PTX 987 at 93-95; PTX 988 at 3.)

2) Molecular Weight

Sandoz's proposed product has a specification for peak average molecular weight between 5,000 and 9,000 daltons. (Sept. Tr. (Grant) 222:6-17.) As set forth in Figure 16 below, the data in Sandoz's ANDA demonstrates that each of its lots falls within the specified 5,000-9,000 daltons range. (Sept. Tr. (Grant) 222:6-17; PTX 349 at SDZ00017949; PTX 351 at SDZ00018608-611; PTX 986 at 26.)

Figure 16

[redacted]	[redacted]
077K7277	8407
087K7253	7275
058K7278	7216
078K7276	7104
128K7276	5932
029K7279	7641
049K7275	6977
049K7276	7366
059K7275	7199
CT0743	8274
CT0750	7417

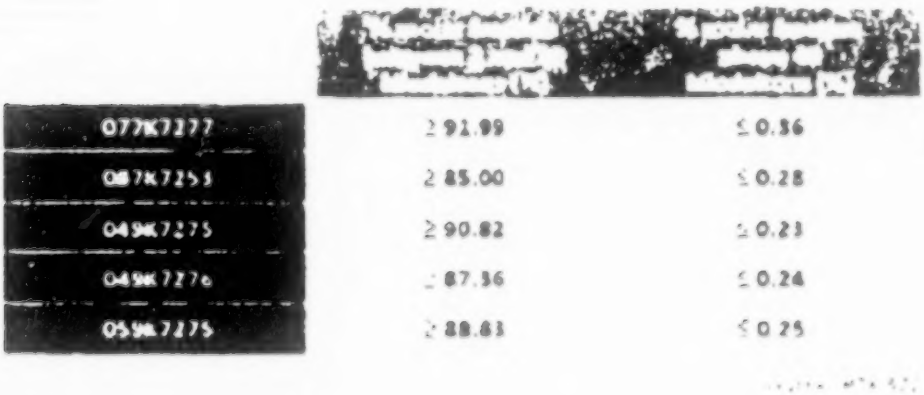
[redacted]

Sandoz determined these peak molecular weight values using SEC with TSK gel G 3,000 and G 2,000 columns. (Sept. Tr. (Grant) 214:19-215:5.) Sandoz calibrated the SEC columns using nine peptide

standards that (i) had amino acid compositions consistent with the composition of copolymer-1 and (ii) had the same size-to-molecular weight relationship as copolymer-1. (Sept. Tr. (Grant) 215:6-13.) In addition to having a specified peak molecular weight, Sandoz's product also has particular molecular weight distribution characteristics, some of which are shown in Figure 17 below. (Sept. Tr. (Grant) 230:13-233:14; PTX 986 at 33.)

Dr. Grant used electronic molecular weight data generated by Sandoz, during its SEC measurements of five Sandoz drug substance lots, to calculate the percentage (on a molar fraction basis) of the copolymer-1 molecules in each lot that have a molecular weight between 2 and 20 kilodaltons and the percentage having molecular weights above 40 kilodaltons. (Sept. Tr. (Grant) 230:13-233:14.) These percentages are listed in Figure 17 below.

Figure 17

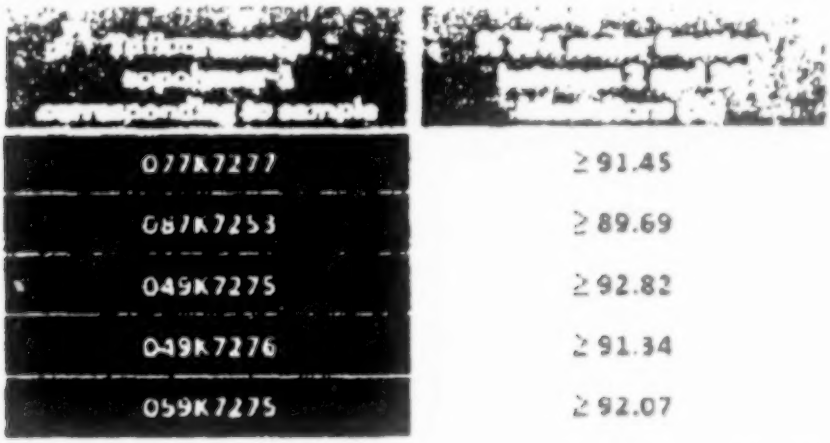


[redacted]	[redacted]	[redacted]
[redacted]	≥ 91.99	≤ 0.36
[redacted]	≥ 85.00	≤ 0.28
[redacted]	≥ 90.82	≤ 0.23
[redacted]	≥ 87.36	≤ 0.24
[redacted]	≥ 88.83	≤ 0.25

Using the electronic molecular weight data for the same five Sandoz drug substance lots, Dr. Grant also calculated the molar fraction percentages of

molecules having molecular weights between 2 and 20 kilodaltons in the TFA copolymer-1 intermediate that corresponded to each lot. (Sept. Tr. (Grant) 236:22-239:4; PTX 986 at 40.) These percentages are listed in Figure 18 below.

Figure 18



ii. Sandoz's Manufacturing Process

Before it entered into the agreement with Momenta, Sandoz worked on developing its own process for making generic Copaxone®. Dr. Anup Ray, a principal scientist at Sandoz and its Rule 30(b)(6) designee on Sandoz's processes for manufacturing copolymer-1, was tasked with this project. (PTX 364 (Topic 18); PTX 966 (Ray Dep.) at 18:13-15, 23:2-24:10, 30:13-16.) The first thing Dr. Ray did after being given his assignment was perform a literature search. (PTX 966 (Ray Dep.) at 32:13-15.) Following the literature search, Dr. Ray's initial strategy was to make generic Copaxone® using the method described in Teva's patent. (PTX 966 (Ray Dep.) at 42:6-15.)

Dr. Ray subsequently began work on developing alternative processes for making generic Copaxone®. (PTX 889; PTX 966 (Ray Dep.) at 81:11-83:20, 108:5-19.) Sandoz's strategy was to develop a route that "circumvented" Teva's patented method. (PTX 123 at SDZ00014130.) Dr. Ray testified he received instructions from a Sandoz lawyer on these alternative processes. (PTX 966 (Ray Dep.) at 127:8-11.)

Dr. Ray eventually devised an alternative process for making copolymer-1 that he concluded was "very different from known Teva patented process." (PTX 115; PTX 117 at SDZ00011436; PTX 966 (Ray Dep.) at 92:6-11.) Sandoz filed a patent application on this process, and Dr. Ray was a named inventor. (PTX 155.) The parties cite no evidence in the record indicating the fate of this patent application.

Momenta's efforts to design a process for making generic Copaxone® were led by Dr. Iyer, who was then a Principal Scientist at Momenta. (PTX 960 (Iyer Dep.) at 5:20-6:9, 16:20-21, 18:3-19:10, 19:20-20:2.) Like Dr. Ray, the first thing Dr. Iyer did when he got his assignment was review the literature on copolymer-1, including the "808 patent. (Sept. Tr. (Bishop) 1075:19-1076:12; PTX 960 (Iyer Dep.) at 19:23-20:2, 147:9-16.) Dr. Iyer understood that Teva's method for making copolymer-1 was a "Patented Process." (PTX 135; PTX 777; PTX 960 (Iyer Dep.) at 452:12-46:19.)

Momenta's process development strategy was set forth in a December 2005 presentation by Dr. Iyer. (PTX 141.) Phase I of the project was to replicate the

"literature process." (PTX 141 at MMT00391608, 610-14.) The "literature process" was Momenta's internal designation for Teva's patented process.[15] (PTX 960 (Iyer Dep.) at 130:7-9, 130:11-14, 130:17.) Phase II was to modify the process to "stay outside the process claims." (PTX 141 at MMT00391608, 647-51.) Phase III was to make further modifications to "add[] additional distance from a[n] IP standpoint." (PTX 141 at MMT00391608, 652-56.)

Steve Brugger, Vice-President of Strategic Product Development for Momenta, acknowledged in a presentation given to Sandoz that there were "[multiple opportunities for development of alternate process." (PTX 119 at MMT01078913; PTX 957 (Brugger Dep.) at 74:19-75:10.)

Dr. Iyer's team worked on replicating the patented "literature process." (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25.) At the same time, Momenta contracted out work on developing a "non-literature process." (PTX 960 (Iyer Dep.) at 32:7-19, 32:21-22, 32:23-25, 33:16-34:8.) Momenta also did its own experimental work on an alternative non-literature process, and eventually filed a patent application on alternative routes for making copolymer-1. (PTX 17 7; PTX 785; PTX 960 (Iyer Dep.) at 159:24-160:18.) Momenta stopped working on an alternative process in 2007, and decided to go forward with filing its ANDA, using Teva's patented process. (PTX 960 (Iyer Dep.) at 37:7-10, 41:6-13, 113:16-19, 127:24-

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[15] At his deposition, Dr. Iyer testified that the "literature" Momenta was following "included everything." (PTX 960 (Iyer Dep.) at 130:7-17.)

128:3, 130:7-17, 138:5-13; PTX 957 (Brugger Dep.) at 78:16-79:23.)

A May 2007 internal Momenta presentation explained Momenta's reasoning for abandoning the development of an alternative, non-infringing process. Momenta decided to file its ANDA using Teva's patented process because it "[e]nable[d] a first-to-file approach" and "[m]itigate[d] risk regarding chemical equivalence." (PTX 172 at MMT01287394.) In other words, as Dr. Iyer explained, Momenta decided to copy Teva's patented process for making copolymer-1 instead of developing its own process because it provided the quickest route to a regulatory filing. (PTX 960 (Iyer Dep.) at 127:18-128:3.) Dr. Iyer further testified that the time of 17 hours and temperature of 26° used in Step 2 of his process—the debenzylation step— was copied out of Teva's patent. (PTX 960 (Iyer Dep.) at 147:17-25, 148:3-7, 148:9-11.)

Broadly speaking, Sandoz's ANDA uses the four-step process described in the patents-in-suit to make its proposed product. In Step 1, as in the patent process, Sandoz combines the N-carboxyanhydrides of alanine, benzyl protected glutamic acid, TFA protected lysine and tyrosine with the initiator diethylamine to form protected copolymer-1, which Sandoz calls Intermediate-1. (Sept. Tr. (Gokel) 348:13-22, 357:2-359:11; PTX 216 at SDZ00001937-38.)

In Step 2, as in the patent process, Intermediate-1 is reacted with HBr/acetic to form TFA protected copolymer-1, which Sandoz calls Intermediate-2.

(Sept. Tr. (Gokel) 359:5-11, 368:4-8; PTX 216 at SDZ00001937-38.) Prior to amending its ANDA on October 27, 2011 (Hagberg Reply Decl. Ex. A, at SDZ00133705-06, SDZ132331-32, SDZ132337-39), Sandoz used the time and temperature of the Step 2 reaction to control the molecular weight of its product and to ensure that it meets the specification of 5,000 to 9,000 daltons. (Sept. Tr. (Gokel) 361:20-363:13; Sept. Tr. (Sampson) 1641:18-1642:8; PTX 213; PTX 214 at SDZ00000186.) Sandoz determined the target time and temperature for Step 2 using "profile runs." (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

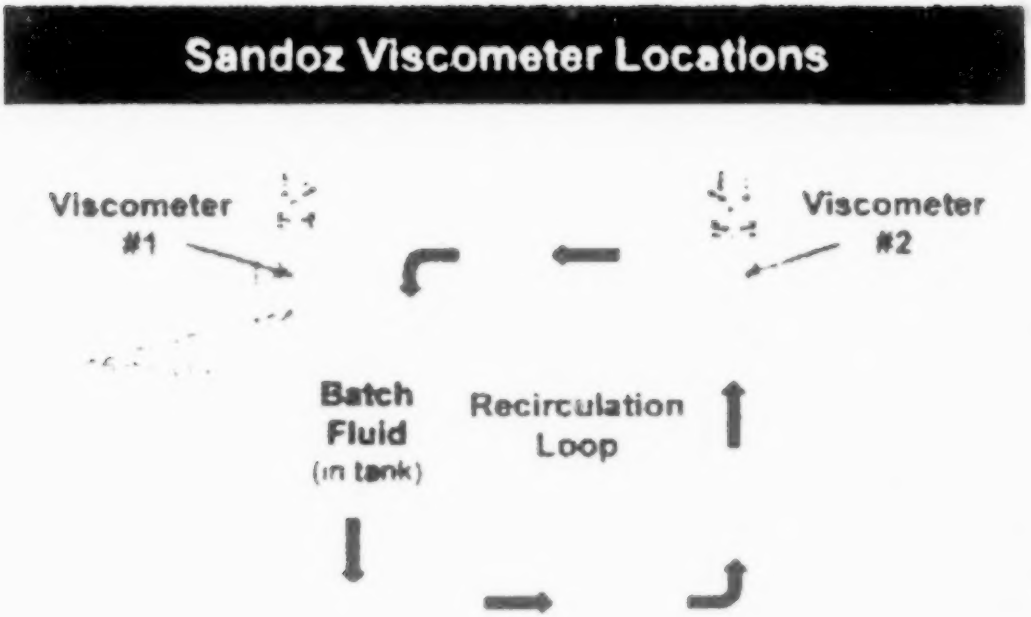
During these profile runs, samples of Intermediate-1 were taken at varying times during the Step 2 HBr/acetic acid reaction. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) The samples were then subjected to Steps 3 and 4 of Sandoz's manufacturing process and converted to glatiramer acetate. The average molecular weights of the resulting batches of glatiramer acetate were determined. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.) With this data, Sandoz was able to determine the window of time for the Step 2 reaction that would allow Sandoz to obtain glatiramer acetate having an average molecular weight between 5,000 and 9,000 daltons. (Sept. Tr. (Gokel) 424:12-425:15; PTX 214 at SDZ00000186.)

The reaction conditions of time and temperature determined from the profile runs were applied to Sandoz's production batches. (Sept. Tr. (Gokel) 424:12-425:15; Sept. Tr. (Bishop) 1098:16-1099:6; PTX 214 at SDZ00000186.) Sandoz ran Step 2 for 43-

47 hours at a temperature of 20 ± 2°C. (Sept. Tr. (Bishop) 1098:1-1099:6; PTX 353 at SDZ00017631-32.)

In its [redacted] ANDA amendment, Sandoz and Momenta represented that they have ceased using a time and temperature model. Sandoz and Momenta currently employ an in-process viscometry method to determine the endpoint of their HBr/acetic acid Step 2 depolymerization reaction. (Hagberg Reply Decl. Ex. A at SDZ00133705-06, SDZ132331-32, SDZ132337-39.) At trial, Dr. Laird explained that, in this model, a viscometer is inserted into a tank in which the depolymerization reaction takes place, where it "measures the viscosity and also measures the temperature ... at the same point at which the viscosity is measured." (Sept. Tr. (Laird) 1131:14-23.) A second, back-up viscometer is inserted into a recirculation loop, where it measures both viscosity and temperature at a different location in the reaction tank from the first viscometer." (Sept. Tr. (Laird) 1131:24-1132:3.) Sandoz's in process method is depicted in Figure 19 below.

Figure 19



(DTX 3580 at 4.)

Viscosity is a property that describes the fluidity of a solution. (Sept. Tr. (Gokel) 427:7-11.) For example, gasoline and water have a low viscosity, whereas honey has a high viscosity. (Sept. Tr. (Gokel) 427:7-11.) The premise of the viscometer model is that the viscosity of an Intermediate-1 sample at a given temperature can be correlated with the average molecular weight of the final glatiramer acetate product. (Sept. Tr. (Gokel) 426:3-427:6; PTX 913 at 36.) The Step 2 HBr/acetic acid reaction is stopped when a viscosity is reached that provides a final glatiramer acetate product having the targeted average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 432:11-23; PTX 914 at MMT01630953.)

Sandoz previously determined the Intermediate-1 viscosity values that would give the glatiramer acetate final product with the targeted average molecular weight of 7,300 daltons using test reactions. In these test reactions, samples of Intermediate-1 were reacted with HBr/acetic acid at varying times and temperatures, and the viscosity values were measured. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.) The samples of Intermediate-1 were then converted to glatiramer acetate, and the average molecular weights of the glatiramer acetate samples were determined. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-114.)

Using this data, Sandoz determined what viscosity value of Intermediate-1 at a given temperature would result in final glatiramer acetate product having an average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-14.) Sandoz took the viscosity and temperature information it obtained and created a table of predetermined targeted viscosity values for given reaction temperatures. (Sept. Tr. (Gokel) 436:18-439:6; PTX 928 at MMT01707035.) The table contains temperatures ranging from 20.0°C to 24.0°C, in increments of two tenths of a degree, and their corresponding targeted viscosity values. (Sept. Tr. (Laird) 1159:19-1160:3; PTX 928 at MMT01707035.) The Step 2 reaction is stopped when the targeted viscosity value is reached for the Step 2 reaction temperature. (Sept. Tr. (Gokel) 430:17-431:24; PTX 914 at MMT01630952-53; PTX 928 at MMT01707035.)

Momenta documents indicate that as time increases, viscosity decreases. (PTX 914 at MMT01630951-53.) Thus, the longer Intermediate-1 reacts with HBr/acetic acid, the lower its viscosity. This enables Sandoz to use viscosity, which changes as a function of time, rather than time itself, to monitor the progress of the reaction and determine when to stop it in order to obtain glatiramer acetate having an average molecular weight of 7,300 daltons. (Sept. Tr. (Gokel) 430:7-16, 434:9-17.)

In Step 3 of the Sandoz and patent processes, Intermediate-2 is treated with piperidine, which removes the TFA protecting groups from the lysines. (Sept. Tr. (Gokel) 359:17-360:9, 368:9-13; PTX 216 at SDZ00001937-38.) Sandoz's ANDA refers to the resulting product as Intermediate-3. In Step 4, the final step of both the Sandoz and patent processes, Intermediate-3 is purified by a step called diafiltration. During this step, acetic acid is used. (Sept. Tr. (Gokel) 360:3-18, 361:3-19; PTX 216 at SDZ00001937-38, 949.) The product of Step 4 is glatiramer acetate, or copolymer-1. (Sept. Tr. (Gokel) 360:3-18; PTX 216 at SDZ00001937-38.)

iii. Sandoz's ANDA Product Label

The proposed label for Sandoz's ANDA product has the identical indication and dosage information as Teva's Copaxone® label. (Sept. Tr. (Lisak) 141:13-145:6; PTX 206 at SDZ00000034, 044; PTX 697.) Sandoz's proposed product label states that the product is "indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis." (Sept. Tr. (Lisak) 141:13-145:6;

PTX 206 at SDZ00000034.) If Sandoz's ANDA product is approved by the FDA, its use would comprise a method of treating multiple sclerosis (Sept. Tr. (Lisak) at 145:21-146:1, 146:23-147:1), and Sandoz's proposed label would encourage physicians to use the ANDA product to treat patients with multiple sclerosis. (Sept. Tr. (Lisak) 147 :16-19.)

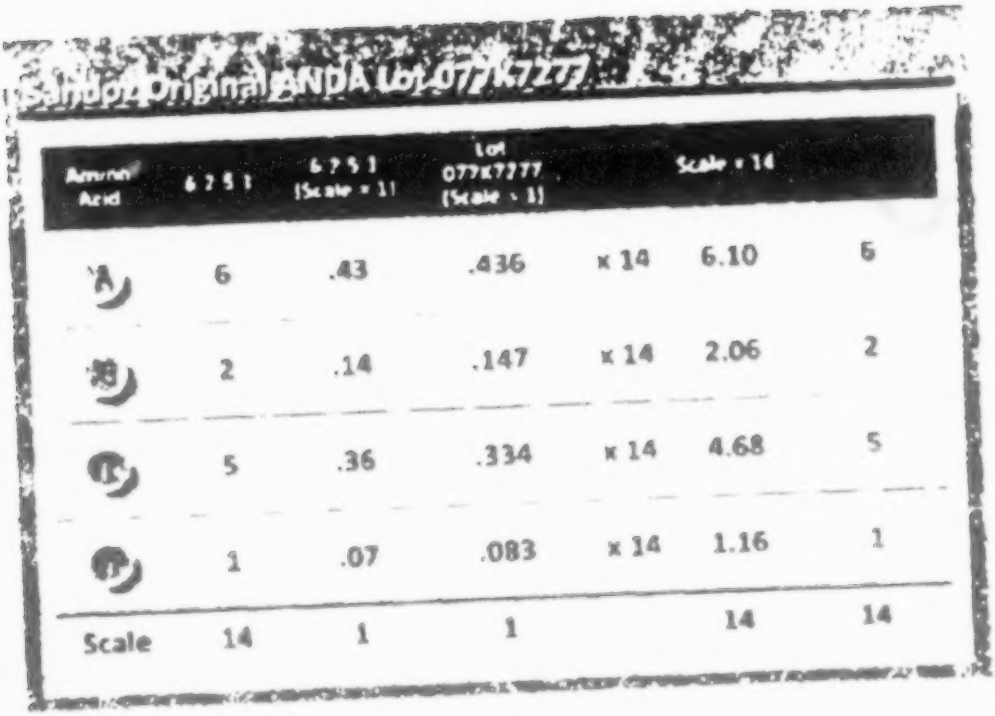
E. Conclusions of Law as to Sandoz's Product

i. Sandoz's Proposed Product Infringes Each of the Asserted Claims because Sandoz's Product is Copolymer-1

Up to the eve of trial, Sandoz did not dispute that its proposed generic product was copolymer-1. Then, in its pretrial submissions, Sandoz argued, for the first time, that its proposed product is not copolymer-1 because it does not have an amino acid molar ratio of approximately 6:2:5:1. Sandoz's argument lacks merit.

As explained above, Sandoz's ANDA provides molar fraction data for its proposed product. At trial, Dr. Gokel testified that when Sandoz's molar fraction data and "6:2:5:1" are compared on the same scale, it is plain that Sandoz's molar ratio is approximately 6:2:5:1. (Sept. Tr. (Gokel) 417:14-421:16; PTX 987 at 90.) This can be seen in Figure 20 below. Dr. Gokel's testimony, which the Court credits, was unrebutted.

Figure 20

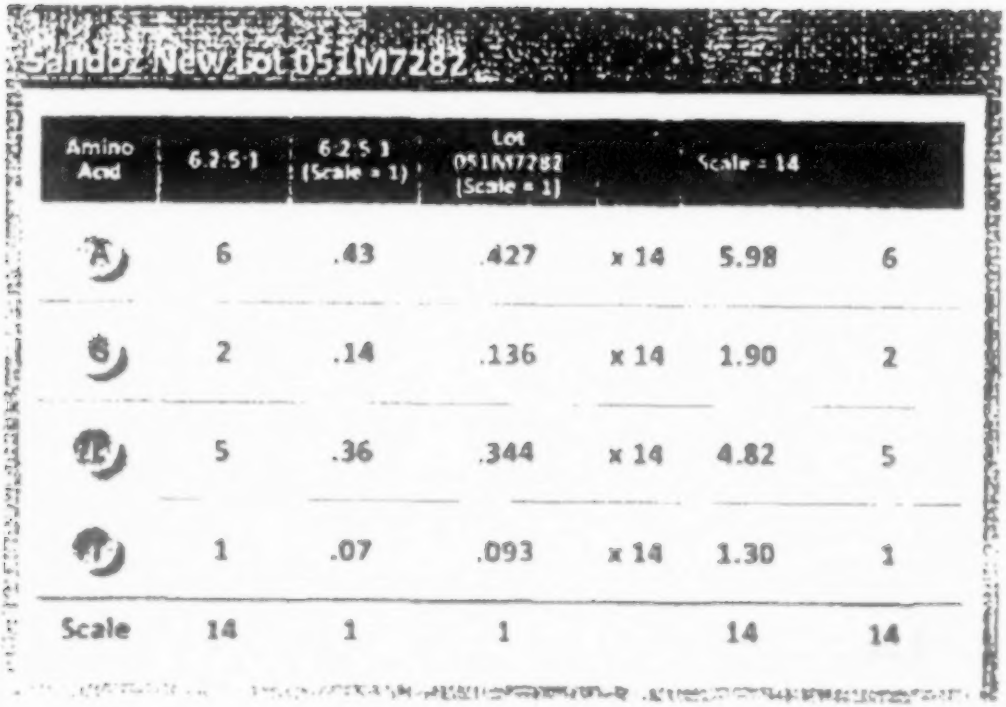


Sandoz Original ANDA Lot 077K7277

Amino Acid	6751	6751 (Scale = 1)	Lot 077K7277 (Scale = 1)		Scale = 14	
A	6	.43	.436	x 14	6.10	6
B	2	.14	.147	x 14	2.06	2
C	5	.36	.334	x 14	4.68	5
D	1	.07	.083	x 14	1.16	1
Scale	14	1	1		14	14

Contrary to what Sandoz argues, the result is no different if the new data from Sandoz's [redacted] Briefing Book is considered. At trial, Dr. Gokel testified that the molar ratio in Sandoz's new lot is approximately 6:2:5:1. (Sept. Tr. (Gokel) 420:3-422:15; PTX 987 at 95.) This can be seen in Figure 21 below. This testimony, which the Court also credits, was also unrebutted.

Figure 21



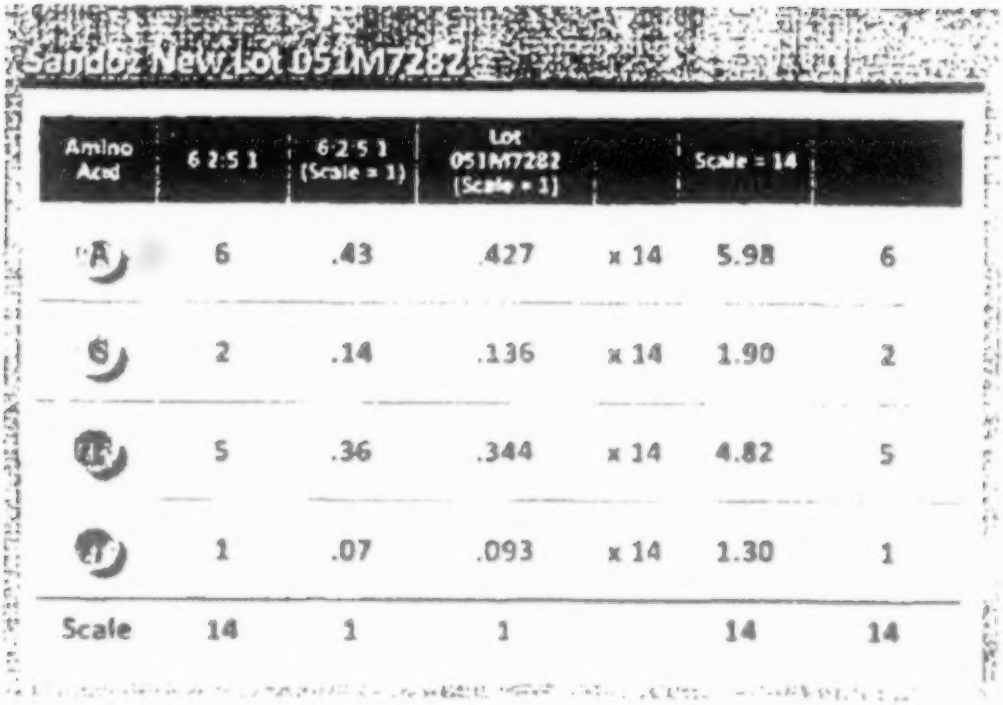
Sandoz New Lot 051M7282

Amino Acid	6:2:5:1	6:2:5:1 (Scale = 1)	Lot 051M7282 (Scale = 1)		Scale = 14	
A	6	.43	.427	x 14	5.98	6
G	2	.14	.136	x 14	1.90	2
[illegible]	5	.36	.344	x 14	4.82	5
[illegible]	1	.07	.093	x 14	1.30	1
Scale	14	1	1		14	14

Sandoz's proposed product therefore literally meets the limitation of "approximately 6:2:5:1" and is copolymer-1 within the meaning of the asserted claims. Moreover, even if Sandoz's product did not literally meet the requirement of a molar ratio of "approximately 6:2:5:1," it would meet that requirement under the doctrine of equivalents.

As shown below in Figure 22, the percent total difference in amino acid ratios between Sandoz's product and exactly 6:2:5:1 is 4.4%. (Sept. Tr. (Sampson) 546:21-547:22; PTX 988 at 3.) For the reasons discussed above with respect to Mylan's product, Sandoz's proposed product is equivalent to approximately 6:2:5:1.

Figure 22



Sandoz New Lot 051M7282

Amino Acid	6 2:5 1	6:2:5 1 (Scale = 1)	Lot 051M7282 (Scale = 1)		Scale = 14	
A	6	.43	.427	x 14	5.98	6
S	2	.14	.136	x 14	1.90	2
[illegible]	5	.36	.344	x 14	4.82	5
[illegible]	1	.07	.093	x 14	1.30	1
Scale	14	1	1		14	14

ii. Sandoz's Product Meets the Molecular Weight Limitations

At trial, Dr. Grant explained why Sandoz's ANDA product meets the molecular weight limitations of each of the asserted claims. (Sept. Tr. (Grant) 265:2-268:3.) Sandoz did not offer any testimony to rebut Dr. Grant's conclusions.

1) Average Molecular Weight Limitations

Sandoz's method for determining the peak molecular weight values of its product involves using an appropriately calibrated suitable gel filtration column. (Sept. Tr. (Grant) 212:4-218:17; PTX 209 at SDZ00002017.) Based on Dr. Grant's testimony, which the Court credits, and the peak molecular

weight data in Sandoz's ANDA, Sandoz's proposed product meets the molecular weight limitations of claim 1 of the "808 patent and claim 1 of the '589 patent, which require a copolymer-1 having an average molecular weight of "about 5 to 9 kilodaltons"; claims 1 and 6 of the x847 patent and claims 1, 8, 9, 12, 23, 30, and 31 of the '539 patent, which require a copolymer-1 having an average molecular weight of "about 4 to about 9 kilodaltons"; and claim 10 of the x539 patent, which requires a copolymer-1 with an average molecular weight of "6.25 to 8.4 kilodaltons." (Sept. Tr. (Grant) 223:20-225:2.)

2) Sandoz's Proposed Post-Trial Claim Construction

In its post-trial claim construction briefing, Sandoz asks the Court to modify the claim construction of all claims with a molecular weight limitation to exclude copolymer-1 compositions with a weight average molecular weight of 10 kilodaltons or greater. Sandoz claim construction left two questions unanswered. The first is whether the molecular weight described in the prior art '550 patent was determined by ultracentrifugation. The second is whether the results in the '550 patent referred to weight average molecular weight as opposed to z-average molecular weight. Sandoz contends that the evidence at trial established that the v550 patent was determined by ultracentrifugation and that the results in the '550 patent referred to weight average molecular weight. Based on Teva's statements to the PTO while prosecuting the patents-in-suit, Sandoz argues that the claims exclude copolymer-1 compositions that

have weight average molecular weight greater than 10 kilodaltons.

There is no dispute that a person of ordinary skill in the art would look to the 1971 Teitelbaum article for information regarding the '550 patent. At trial, Dr. Scandella testified that, based on the 1971 Teitelbaum article, a person of ordinary skill in the art would understand that the '550 patent's reference to copolymer-1 with a molecular weight of 10 kilodaltons refers to molecular weight determined by ultracentrifugation. (Sept. Tr. (Scandella) at 1288:9-1290:2.) He testified further that the particular type of ultracentrifugation described in the 1971 Teitelbaum article— using sedimentation and diffusion measurements from a Spinco model E ultracentrifuge—would provide weight average molecular weight. (Sept. Tr. (Scandella) at 1290:6-10.) Because Teva allegedly disclaimed copolymer-1 compositions with weight average molecular weights in excess of 10 kilodaltons during the prosecution history of some of the patents-in-suit, Sandoz contends that all of the claims with a molecular weight limitation should exclude copolymer-1 compositions with a weight average molecular weight of 10 kilodaltons or greater. Under this claim construction, Sandoz argues, its proposed product does not infringe the patents-in-suit because its proposed product has a weight average molecular weight greater than 10 kilodaltons.

As an initial matter, Sandoz has produced batches of copolymer-1 with a weight average molecular weight lower than 10 kilodaltons. (PTX 913-R at 53; PTX 349-R at 55.) To the extent Sandoz argues that

the weight average molecular weight of its lots will be different when marketed, Sandoz offers nothing but the conclusory statements of its attorneys. The Court gives no weight to these assertions.

With respect to Dr. Scandella's trial testimony, it is undisputed that his expert reports were silent regarding the type of average molecular weight that could be obtained from a Spinco model E centrifuge. Pursuant to Rule 26(a)(2)(B)(i) of the Federal Rules of Civil Procedure, an expert's report "must contain . . . a complete statement of all opinions the witness will express and the basis and reasons for them." Fed. R. Civ. P 26(a) (2) (B) (i). Courts have routinely excluded expert testimony in cases such as this. See, e.g., Silivanch v. Celebrity Cruises, Inc., 171 F. Supp. 2d 241, 256-57 (S.D.N.Y. 2001).

Further, the Court has no doubt that Teva was prejudiced by its inability to examine the basis of Dr. Scandella's opinion at his deposition or to elicit more specific testimony from its own experts to counter Dr. Scandella's opinion. Nonetheless, the Court will not strike Dr. Scandella's testimony because the Court credits Dr. Grant's cross-examination testimony that ultracentrifugation can yield, "among others," number average molecular weight and z-average molecular weight. (Sept. Tr. (Grant) 1483:25-1484:21, 1488:9-11.) Mylan's expert, Dr. Ryu, also opined, during claim construction, that ultracentrifugation could provide z-average molecular weight, in addition to weight average molecular weight. (Dkt. 273 at 43.)

In regard to Dr. Scandella's claim that a person of ordinary skill in the art would understand that the '550 patent's reference to a copolymer-1 with a molecular weight of 10 kilodaltons refers to molecular weight determined by ultracentrifugation based on the 1971 Teitelbaum article (Sept. Tr. (Scandella) 1288:9-1290:2), Dr. Grant and Dr. Zeiger both testified that the reference to 10 kilodaltons in the '550 patent does not refer to copolymer-1. (Sept. Tr. (Grant) 1435:2-15, 1436:5-16; Sept. Tr. (Zeiger) 930:21-932:12.) The Court credits the testimony of Dr. Grant and Dr. Zeiger.

To the extent Sandoz rehashes its argument about Teva's statements to the PTO, in view of Sandoz's failure to offer any new evidence on this point, there is no basis for the Court to revisit its finding that Teva's prosecution history statements did not "clearly and unambiguously express surrender of copolymer-1 with a weight average molecular weight greater than 10 kilodaltons." (CCO at 42 (quoting Sorensen v. Int'l Trade Comm'n, 427 F.3d 1375, 1378 (Fed. Cir. 2005).) Lastly, to the extent Sandoz again points the Court to the testimony of Dr. Arnon, Dr. Sela, and Dr. Pinchasi regarding the molecular weights described in the '550 patent, as the Court previously found and as Sandoz itself admits, their testimony was not available to those of ordinary skill in the art in 1994. (CCO at 43.)

For the reasons provided above, the Court rejects Sandoz's proposed post-trial claim construction.[16]

3) Copolymer-1 Molar Fraction Limitations

Based on Dr. Grant's calculations, which the Court credits, Sandoz's proposed product meets the molecular weight limitations of claims 1, 2 and 3 of the M30 patent, which require the copolymer-1 to have over 75% of its molar fraction within the molecular weight range of 2 and 20 kDa; claims 8 and 30 of the '539 patent, which require the copolymer-1 to have less than 2.5% of its molar fraction with molecular weights above 40 kDa; claims 9, 10, and 31 of the '539 patent and claim 8 of the '098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 2.5% of its molar fraction with molecular weights greater than 40 kDa; claim 1 of the '476 patent, claim 1 of the '161 patent, and claim 1 of the '098 patent, which require that the copolymer-1 have over 75% of its molar fraction between the molecular weights of 2 and 20 kDa and less than 5% of its molar fraction with molecular weights greater than 40 kDa. (Sept. Tr. (Grant) 233:23-235:2.)

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[16] To the extent Sandoz attempts to poke holes in the Court's construction of "average molecular weight" as "peak molecular weight" in its proposed post-trial claim construction, Sandoz does not ask the Court to construe "average molecular weight" differently.

4) TFA Copolymer-1 Molar Fraction Limitations

Based on Dr. Grant's calculations, which the Court credits, Sandoz's proposed product meets the molecular weight limitations of claims 1, 2, and 3 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent, which require that the TFA copolymer-1 that is made as a result of treatment of protected copolymer-1 with hydrobromic acid have over 75% of its molar fraction with molecular weights between 2 and 20 kDa. (Sept. Tr. (Grant) 239:11-240:8.)

iii. Sandoz's Process Meets the Process Limitations

With the exception of the "predetermined by test reaction" limitation, Sandoz has not disputed that the manufacturing process in its ANDA meets the process limitations of the asserted claims. Based on Dr. Gokel's testimony, which the Court credits, and the information in Sandoz's ANDA, Sandoz's process meets the "reacting protected copolymer-1 with hydrobromic acid" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1 and 2 of the '898 patent, claims 1 and 2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the "161 patent; the "treating trifluoroacetyl copolymer-1" limitation found in claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1, 2, and 3 of the '898 patent, claims 1, 2, and 3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, and claims 1 and 6 of the '847 patent; the "purifying" limitation found in claim 1 of the '808 patent, claim 1

of the '589 patent, and claims 1 and 6 of the '847 patent; the "selecting a predetermined molecular weight profile" limitation of claims 1, 2, and 3 of the '898 patent; and the "copolymer-1 fraction" limitations of claim 1 of the '161 patent and claim 1 of the '476 patent. (Sept. Tr. (Gokel) 349:4-350:18, 354:16-363:13, 447:20-469:7.)

iv. Sandoz's Viscometer Process Meets the Test Reaction Limitations

Sandoz's viscometer process comprises a table of temperatures and viscosity values. (Sept. Tr. (Gokel) 430:7-434:22; PTX 914 at MMT01630951-52; PTX 928 at MMT01707035.) These data are based on test reactions, as the Court has construed that term. (Sept. Tr. (Gokel) 436:18-439:10; PTX 923 at MMT01694006, 106-24.) At trial, Dr. Laird agreed that these data were obtained from test reactions. (Sept. Tr. (Laird) 1160:4-8.)

The temperature in the viscometer model is predetermined, as there is a pre-set temperature target of 21°C. The viscometer model also has a column that identifies particular temperatures in tenths of a degree. (Sept. Tr. (Gokel) 432:11-23, 435:14-436:3; PTX 914 at MMT01630954-55; PTX 928 at MMT01707035-36.)

Time is predetermined according to the viscometer model because there is a predetermined relationship between time and viscosity. As Dr. Gokel testified, "Sandoz Momenta determined .. a relationship between time and viscosity and then used that to determine the end point for Step 2." (Sept Tr. (Gokel)

434:9-17.) "Viscosity reflects the time point at which the reaction should be stopped because" Sandoz "calibrated their systems so that the viscosity correlates." (Sept Tr. (Gokel) 515:8-10; see also 518:14-17 ("My understanding is that the end point for the viscosity measurement corresponds to the time the reaction needs to run at a specified temperature so that the desired molecular weight structure will be obtained.").) While Sandoz may be correct that an operator could not know "with complete certainty" that after a certain time period a targeted viscosity level would be reached, if the operator "has the time correlation, then he or she could know . . what time that correlates to in terms of the viscosity"; albeit, not with "complete certainty." (Sept Tr. (Gokel) 519:12-18.)

The Court finds that Sandoz's overall process for determining when to stop the HBr/acetic acid reaction in order to obtain a copolymer-1 having an average molecular weight of 7,300 daltons is insubstantially different from the process claimed in the patents-in-suit. See Adams Respiratory Therapeutics, Inc. v. Perrigo Co., 616 F.3d 1283, 1293 (Fed. Cir. 2010) ("The proper inquiry is whether the accused value is insubstantially different from the claimed value."); Boehringer Ingelheim Vetmedica, 320 F.3d at 1351 ("Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art.") (citations omitted).

Determining when to stop the reaction in order to obtain a copolymer-1 having an average molecular

weight of 7,300 daltons by using test reactions to predetermine a relationship between temperature, viscosity, and time to stop the reaction is insubstantially different from using test reactions to predetermine a pre-set time to stop the reaction. In either case, a copolymer-1 having an average molecular weight of 7,300 daltons is obtained. To the extent that "[a] viscometer is different from a clock" (Sept. Tr. (Gokel) 517:1-4), Sandoz's process simply uses viscosity as a surrogate for time in order to ensure that it achieves the predetermined 7,300 daltons average molecular weight. (Sept. Tr. (Gokel) 436:18-439:6; PTX 923 at MMT01694006, 106-14; see also Sept. Tr. (Laird) 1132:10-16.) Given Sandoz's correlation of time, temperature, viscosity, and average molecular weight, its viscometer method for determining when to stop the Step 2 reaction is only insubstantially different from the claimed method of using time to determine when to stop the reaction. (Sept. Tr. (Gokel) 430:7-16, 434:9-17, 436:4-17.) Sandoz's predetermined viscosity values serve the same purpose, and achieve the same result, as the predetermined time limitation in the claims. (Sept. Tr. (Gokel) 430:17-431:15, 432:10-23, 433:24-434:17.)

Thus, under the doctrine of equivalents, Sandoz's viscometer model meets the "predetermined by test reaction" limitation in claims 1-2 of the '898 patent, claims 1-2 of the '430 patent, claim 1 of the '476 patent, and claim 1 of the '161 patent. In addition, because Sandoz's process targets a temperature of 21°C and can range only from 20.0°C to 24.0°C, the temperature limitation ("about 20-28°C") of claim 2 of the '898 patent and claim 2 of the '430 patent is met.

v. Sandoz Meets the Treatment Limitations

Based on Dr. Lisak's testimony, which the Court credits, Sandoz's proposed product meets the "method of treating multiple sclerosis" limitation found in claim 1 of the '476 patent; the "administering to a subject in need thereof" limitation found in claim 1 of the '476 patent; the "pharmaceutically effective amount" limitation found in claim 1 of the ' 476 patent and claim 1 of the '161 patent; the "treatment of multiple sclerosis" limitation found in claim 1 of the '161 patent; the "suitable for treating multiple sclerosis" limitation found in claim 1 of the '539 patent; the "dose therapeutically effective to treat multiple sclerosis" found in claim 12 of the v539 patent; the "a method for treating a patient suffering from multiple sclerosis" found in claims 23, 30, and 31 of the '539 patent; the "administering to a patient in need thereof" limitation found in claims 23, 30, and 31 of the "539 patent; and the "suitable for treating multiple sclerosis" limitation found in claim 1 of the x098 patent. (Sept. Tr. (Lisak) 137:5-147:19; PTX 985 at 20.)

In addition, based on the stipulation entered into by Sandoz, Sandoz's proposed product meets the limitations of "pharmaceutical composition" and "pharmaceutically acceptable excipient" in claims 12, 23, 30, and 31 of the '539 patent. (PTX 936.)

Finally, Sandoz would induce physicians to infringe the '476 and '539 patents if its ANDA were approved. Sandoz knew of those patents before filing its ANDA, as it filed a certification with the FDA and sent a notice letter to Teva specifically referencing the patents-in-suit, including the 476 and "539 patents. (PTX 254 at SDZ00016843; JPO ¶¶ 89-90, 94-95.) Sandoz's proposed product label would induce doctors to prescribe its ANDA product for treatment of multiple sclerosis and thereby induce infringement of claim 1 of the "476 patent and claims 23, 30, and 31 of the '539 patent. See AstraZeneca LP, 633 F.3d at 1060 ("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [the alleged infringer's] affirmative intent to induce infringement.") (citations omitted).

vi. Sandoz Infringes All of the Asserted Claims

In conclusion, based on the testimony of Dr. Lisak, Dr. Grant, Dr. Sampson, and Dr. Gokel, the documentary evidence they referred to during their testimony, and Sandoz's stipulations, the Court finds, by a preponderance of the evidence, that Sandoz's manufacture and sale of its proposed glatiramer acetate product would infringe each of the asserted claims.

II. INVALIDITY DEFENSES

A. Best Mode

Mylan, but not Sandoz, argues that the patents-in-suit are invalid for violating the best mode requirement of 35 U.S.C. § 112. It argues that inventor Eliezer Konfino failed to disclose: (a) the use of phenol as a bromine scavenger in the claimed synthetic process and (b) copolymer-1 with "low bromotyrosine" amounts. Mylan also argues Teva is judicially estopped from arguing that making low bromotyrosine copolymer-1 using phenol was a routine detail that would have been obvious to a person of ordinary skill in the art in 1994.

Mylan and Teva agree that if Mylan's best mode defense were successful, it would invalidate the only claim in each of the following patents: the '808 patent, the '589 patent, the '476 patent, and the '161 patent. Mylan contends that if its best mode defense were successful, it would also invalidate all of the claims in the '898 patent and the '430 patent, because all of the claims recite the step of using HBr in the preparation of copolymer-1. Teva disagrees, arguing that if Mylan's best mode defense were successful, it would only apply to claims 1, 2, and 3 of both the '898 patent and the '430 patent. Mylan also contends that if its best mode defense were successful, it would invalidate claims 2, 3, 4, 5, and 8 of the '847 patent, because these claims recite the step of using HBr in the preparation of copolymer-1. Lastly, there is no disagreement that Mylan's best mode defense does not implicate the '539 patent or the '098 patent. Because the Court finds that Mylan

has failed to establish its best mode defense by clear and convincing evidence, any disagreement between Teva and Mylan regarding the claims that are implicated by Mylan's best mode defense are irrelevant.

i. General Principles

"Section 112 of the Patent Act provides that the patent specification 'shall set forth the best mode contemplated by the inventor of carrying out his invention." Ajinomoto Co., Inc. v. Int'l Trade Comm'n, 597 F.3d 1267, 1272 (Fed. Cir. 2010) (quoting 3 5 U.S.C. § 112, ¶ 1). To comply with the best mode requirement, "an inventor must disclose the preferred embodiment of his invention as well as preferences that materially affect the properties of the invention." Id. at 1272-73 (citation omitted). The requirement is limited, however, "to 'the invention defined by the claims. "Id. at 1273 (citations omitted). As a result, the "threshold step in a best mode inquiry is to define the invention by construing the claims." Id. (citation omitted). Here, that has already been done.

Since the invention has been defined, the Court turns to the two-prong inquiry for determining compliance with the best mode requirement. The Court must first "determine whether, at the time the patent application was filed, the inventor possessed a best mode of practicing the claimed invention." Ajinomoto Co., 597 F.3d at 1273 (citation omitted). This prong is subjective and "focuses on the inventor's own personal preferences as of the application's filing date." Id. (citation omitted). "[I]f

the inventor has a subjective preference for one mode over all others," the Court must, second, "determine whether the inventor 'concealed' the preferred mode from the public." Id. (citation omitted). The second prong "asks whether the inventor's disclosure is adequate to enable one of ordinary skill in the art to practice the best mode of the invention." Id. (citation omitted). "This second inquiry is objective, depending on the scope of the claimed invention and the level of skill in the relevant art." Wellman, Inc. v. Eastman Chem. Co., 642 F.3d 1355, 1360 (Fed. Cir. 2011) (citation omitted).

The Federal Circuit has repeatedly explained that "[t]he best mode requirement does not require the disclosure of 'routine details' that would be apparent to one of ordinary skill in the art practicing the invention." Liquid Dynamics Corp. v. Vaughn Co., Inc., 449 F.3d 1209, 1223 (Fed. Cir. 2006) (citation omitted). "The best mode requirement" also "does not extend to 'production details,' including commercial considerations such as equipment on hand, availability of materials, relationships with suppliers, or customer requirements." Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1331 (Fed. Cir. 2002) (citations omitted).

Mylan bears the burden of establishing a violation of the best mode requirement with clear and convincing evidence. See, e.g., Id.

ii. The Use of Phenol to Pre-treat HBr/Acetic Acid

Eliezer Konfino was the only inventor named on the patents-in-suit involved in the development of the claimed synthetic process, which was used to consistently and reproducibly produce a lower molecular weight copolymer-1. (July Tr. (Pinchasi) 66:16-68:25; PTX 1 at 4:29-6:3; DTX 3567 (Konfino Dep. Tr.) at 60:8-63:9, 182:9-19, 184:6-11; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 20:3-21:11.) Konfino, a bench chemist, was involved in development activity, but was not involved in manufacturing copolymer-1 on a commercial scale. (Sept. Tr. (Kent) 761:20-23, 1736:22-25; DTX 3567 (Konfino Dep.) at 25:8-23, 28:18-24; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 18:6-18, 20:3-11.) He retired and ceased all involvement with copolymer-1 development in 1991. (PTX 3567 (Konfino Dep.) at 29:14-19, 34:11-14, 39:2-5, 117:2-15.)

In some experiments, Konfino used a reagent called phenol to pre-treat the HBr/acetic acid he used during the debenzylation step of the synthetic process he was developing. (DTX 3567 (Konfino Dep.) at 113:17-114:21.) During these experiments, he used phenol to reduce or "scavenge" free bromine from the HBr/acetic acid he was using as part of the debenzylation reaction. (DTX 3567 (Konfino Dep.) at 113:17-114:5.) As explained above, free bromine present in HBr/acetic acid can react with tyrosine moieties to form an impurity known as bromotyrosine. (Sept. Tr. (Gokel) 1597:24-1600:23; Sept. Tr. (Owens) 631:21-632:6; Sept. Tr. (Kent) 771:19-23.) Reducing the presence of free bromine

can, as a result, reduce amounts of bromotyrosine in copolymer-1. (Sept. Tr. (Owens) 611:15-25; Sept. Tr. (Kent) 666:16-24.) At the time Mr. Konfino was developing his synthetic process, Teva's specification for bromotyrosine content in copolymer-1 was less than 0.5%. (Sept. Tr. (Kent) 1736:15-17; PTX 52 at TEV1177354-57; DTX 1270 at 211.)

Although he used phenol in some experiments, in many others, Konfino did not use phenol to scavenge free bromine. (Sept. Tr. (Kent) 761:20-762:2, 762:23-765:25, 1737:1-4; PTX 52 at TEV1177220, TEV1177226-27, TEV1177352-33, TEV1177354.) Indeed, in experiments conducted in March 1991—the last month for which his lab notebooks report copolymer-1 experiments before his retirement—Konfino used HBr/acetic acid from the same supplier, once with phenol and once without phenol and in each case obtained copolymer-1 with bromotyrosine amounts that were within Teva's less than 0.5% specification. (Sept. Tr. (Kent) 763:25-765:25; PTX 52 at TEV1177354-57.) Konfino also obtained copolymer-1 and TFA copolymer-1 with a bromotyrosine content of less than 0.5% in a number of other experiments in which he did not use phenol. (Sept. Tr. (Kent) 761:24-762:2, 762:23-765:25, 1737:1-4; PTX 52 at TEV1177220, TEV1177226-27, TEV1177352-33, TEV1177354.) Until he left Teva in 1991, Konfino continued to make copolymer-1 without the use of phenol. (Sept. Tr. (Kent) 762:3-11.)

Konfino never considered the use of phenol to be part of the synthetic process that he developed. (DTX 3567 (Konfino Dep.) at 113:22-117:15.) At his deposition, he testified:

Q. So you were using phenol to clean hydrobromic acid?

A. I made a lot of experiments that did not become part of the process, and that's one of them.

* * *

Q. Did you use bromine scavengers in your Copolymer-1 processes?

A. Not in my process.

Q. In your process, did you want to get rid of excess bromine?

A. There was no need to.

Q. Why?

A. We changed solvents or we changed other conditions, so there was no need.

* * *

Q. What do you consider to be your process?

A. The process is written down, is described in the patent.

* * *

Q. What differences, if any, are there between the process described in your patent and the process for making Copolymer-1?

A. I believe there is no difference at all[.]

* * *

Q. I'm asking whether you learned more things about the Copolymer-1 process at Teva between your departure in 1991 and your signing of the patent application in 1994?

A. The 1994 patent described my process.

Q. And that was your process as of 1991?

A. The same.

(PTX 3567 (Konfino Dep.) at 113:23-117:15.)

The documents Mylan cited at trial do not support the conclusion that Konfino considered use of phenol to be part of "his process" or a "best" way to make copolymer-1. Mylan's best mode expert, Dr. Kent, cited and gave a considerable amount of attention to a document Konfino authored, stating that pre-treating HBr/acetic acid "with 1% phenol proved to be the most convenient" way to lower the bromotyrosine level of copolymer-1. (PTX 708-T at TEV000324554.) It does not follow, however, that Konfino viewed the use of phenol to be part of his process merely because he described it as "convenient." This is particularly true in view of his testimony, which the Court credits, that he had other means of controlling free bromine available to him. (Sept. Tr. (Kent) 765:17-23; PTX 3567 (Konfino Dep.) at 113:22-117:15.)

In regard to the description of phenol as "the most convenient" method for lowering the bromotyrosine level of copolymer-1, Dr. Kent conceded there are any number of reasons Konfino may have described phenol this way. For example, it could have been "the most convenient" because it was "the nearest [bottle] when [Mr. Konfino] put his hand out to the lab bench." (Sept. Tr. (Kent) 771:13-16.) Another possible, reasonable inference is that phenol was convenient simply because it was the least expensive way of pre-treating HBr/acetic acid. The fact that both of these explanations are entirely plausible effectively proves that the mere characterization of phenol as "the most convenient" means of reducing free bromine does not constitute clear and convincing evidence that it was Konfino's best way of making copolymer-1.

Mylan also points to a manufacturing protocol for copolymer-1 as evidence of Konfino's best mode. (DTX 999 at TEV001222365-RC-387-RC.) Konfino's name appears nowhere in the document, however. (Sept. Tr. (Kent) 765:24-766:8; DTX 999 at TEV001222365-RC-387-RC.) As a result, it has no bearing on Konfino's subjective state of mind—the first prong on the best mode inquiry. Moreover, it is undisputed that Konfino was a bench scientist, who was in no way involved in manufacturing copolymer-1 on a commercial scale. (Sept. Tr. (Kent) 1736:22-25; DTX 3567 (Konfino Dep.) at 25:8-23, 28:18-24; DTX 4019 (Pinchasi 12/21/2009 Dep.) at 18:6-18, 20:3-11.)

Mylan also highlights a 1993 report listing several "major improvements" to the manufacturing process of copolymer-1, one of which reads: "HBr/acetic acid

is treated with phenol before use, thus preventing side reaction of free residual bromine with a tyrosine moiety." (DTX 1270 at TEV000312175.) Like the previous document, however, this document does not list Konfino as an author and was written in 1993—more than a year after Konfino retired and ceased all involvement in the Copaxone® project. (Sept. Tr. (Kent) 766:18-767:5; DTX 1270.) Thus, this document cannot possibly reflect Mr. Konfino's subjective state of mind.

The Court also finds that use of phenol would have been a routine production detail at the time of the patent application. Phenol was readily available in 1994 and was "widely used in peptide chemistry." (Sept. Tr. (Kent) 771:9-16.) It was well known to persons of ordinary skill in the art at the relevant time that some amount of free bromine could be present in HBr/acetic acid depending on the quality or type of HBr/acetic acid used. (Sept. Tr. (Gokel) 1592:14-1593:4; Sept. Tr. (Kent) 754:7-10.) It was also well known at the time that phenol could be used to reduce the presence of free bromine in HBr/acetic acid. (Sept. Tr. (Gokel) 1591:11-1592:13; Sept. Tr. (Kent) 756:5-8; PTX 961 (Kota Dep.) at 130:18-131:18.) Accordingly, use of phenol to reduce the presence of free bromine in HBr/acetic acid would have been a routine production detail at the time of the patent application. (Sept. Tr. (Gokel) 1591:11-1592:13; Sept. Tr. (Kent) 756:5-8; PTX 961 (Kota Dep.) at 130 :18-131:18.)

iii. The Level of Bromotyrosine Impurity

There is also no evidence Konfino viewed any particular level of bromotyrosine copolymer-1 to be part of his invention. Mylan offered no testimony from Konfino on this question. While Konfino recorded making copolymer-1 with a bromotyrosine content that fell below Teva's specification[17] for bromotyrosine at the time—0.5% (Sept. Trial Tr. (Kent) 1736:15-17; PTX 52 at TEV1177354-357; DTX 1270 at 211)—Mylan presented no evidence that Konfino viewed copolymer-1 with a low bromotyrosine content as part of his best mode. Thus, there is no support, much less clear and convincing evidence, from which the Court can find that Konfino subjectively viewed "low bromotyrosine" levels as a requirement for the copolymer-1 he was making.

In addition, the evidence indicates that reducing amounts of bromotyrosine was a routine production detail. Bromotyrosine is an impurity that may be created during the synthetic process used to make copolymer-1. (Sept. Tr. (Gokel) 1603:13-1604:2; Sept. Tr. (Owens) 615:8-16, 634:22-635:8; PTX 349 at SDZ00017963.) All of the experts and parties agree that bromotyrosine is an impurity in the context of

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[17] (See DTX-1271 at TEV000324714 (June 1990 memorandum authored by Konfino and D. Salner, describing making TFA-copolymer-1 with a bromotyrosine content of less than 0.1%); see also PTX-708-T at TEV000324554 (Konfino August 1991 memorandum, reporting he made copolymer-1 with a bromotyrosine content that fell below "the specifications").)

copolymer-1. (Sept. Tr. (Gokel) 1597:24-1600:23, 1603:13-1604:2, 1606:17-1607:18; Sept. Tr. (Kent) 771:19-772:10; Sept. Tr. (Owens) 632:4-633:12; PTX 963 (B. Rao 6/30/2010 Dep.) at 240:7-9; PTX 320 at MYL0000685-86; PTX 349 at SDZ0017963; PTX 78 at TEV000000196.) In fact, bromotyrosine is one of a long list of impurities that are controlled in copolymer-1. (Sept. Tr. (Gokel) 1597:24-1600:23; PTX 78 at TEV000000196-97; PTX 320 at MYL0000685-86.)

There also is no disagreement that it is standard practice within the pharmaceutical industry to reduce impurities in a product. Mylan's expert, Dr. Kent, and fact witness, Dr. Owens, both agreed that reducing impurities like bromotyrosine is standard practice in the pharmaceutical industry. (Sept. Tr. (Kent) 773:3-14; Sept. Tr. (Owens) 633:7-12.) This is consistent with the testimony of Teva's expert, Dr. Gokel, who explained that it would be a "routine matter for anyone trying to make a product at any scale, laboratory, or manufacturing, to try to reduce impurities as much as possible." (Sept. Tr. (Gokel) 1597:18-23; 1607:19-1608:2.)

Mylan cites to U.S. Patent No. 7,495,072 ("'072 patent"), issued in 2009 to inventor Ben Zion Dolitzky and assigned to Teva, as evidence that using phenol to reduce bromotyrosine was not routine. (DTX 1925.) The fact that Teva obtained a patent for a process involving the use of phenol to scavenge free bromine in copolymer-1, Mylan argues, judicially estops Teva from arguing that the use of phenol to scavenge free bromine in copolymer-1 was a routine production detail that would have been

obvious to a person of ordinary skill in the art with respect to the patents-in-suit. Mylan is wrong.

The '072 patent is directed to a solution for a manufacturing problem that arose many years after Konfino left Teva in 1991. (Sept. Tr. (Gokel) 1595:9-15, 1596:23-1597:14.) Specifically, the '072 patent discusses means of using bromine scavengers, including phenol, to eliminate the presence of bromotyrosine and to remove a red color that had been detected in syringes of aqueous solutions of Copaxone®. (Sept. Tr. (Gokel) 1593:8-1594:2, 1594:18-1595:20; DTX 1925 at 10:5-10, 12:41-13:67.) The patent explicitly states that older methods of Copaxone® production—which are not claimed in the '072 patent—used phenol as a bromine scavenger to produce copolymer-1 with reduced levels of bromotyrosine. (Sept. Tr. (Gokel) 1631:7-1633:17; DTX 1925 12:41-13:67.) Thus, the '072 patent is directed to a "new" and improved process that produces Copaxone® with no detectable amounts of bromotyrosine and no red color. (Sept. Tr. (Gokel) 1631:7-1632:21; DTX 1925 at 12:41-13:67.)

At trial, Mylan's expert, Dr. Kent, admitted that the bromotyrosine specification in the '072 patent (0.2% or none detectible) is lower than the specification in place when Konfino was working at Teva (0.5%), providing further evidence that the '072 patent was directed to a different problem and has no bearing on Konfino's experiments. (Sept. Tr. (Kent) 1735:1-1736:17.) Since the '072 patent is directed to a different problem, namely the elimination of bromotyrosine and the removal of an unwanted color from an aqueous form of Copaxone®,

rather than merely reducing bromotyrosine, it does not establish that using phenol to reduce amounts of free bromine was not routine as of 1994.

iv. The Patents' Lack of Disclosure Regarding Phenol Is Not a Best Mode Violation

There is no dispute that the patents-in-suit do not disclose the use of phenol to pretreat HBr/acetic acid used in the debenzylation step of the synthetic process claimed in the patents-in-suit. Defendants have nevertheless failed to prove, by clear and convincing evidence, that this amounts to a best mode violation.

Konfino testified unequivocally that the use of phenol was not part of "his process" at the time he retired from Teva in 1991 and that the process he used is the one described in the patents-in-suit. (PTX 3567 (Konfino Dep.) at 113:22-117:15.) This unambiguous testimony, which the Court credits, is strong evidence that Konfino did not subjectively consider the use of phenol part of his best mode for making copolymer-1. See Minco, Inc. v. Combustion Eng'g, Inc., 95 F.3d 1109, 1116 (Fed. Cir. 1996) (affirming a finding of no best mode violation where the trial court relied on the inventor's testimony that the undisclosed information was a production decision and that he did not consider it to be a superior method of operation); see also Shearing v. Iolab Corp., 975 F.2d 1541, 1546 (Fed. Cir. 1992) (affirming a jury verdict of no best mode violation where the inventor testified that, although he sometimes used the alleged best mode to align the

lens, he had no preference and embraced any method that did so).

The documents relied upon by Mylan at trial reinforce this conclusion. Konfino's lab notebooks indicate he only used phenol in some of his experiments synthesizing copolymer-1, made copolymer-1 without using phenol a number of times, and was still making copolymer-1 without using phenol at the time he left Teva in 1991. The other documents relied upon by Mylan are either irrelevant to Konfino's subjective state of mind or do not support a conclusion that Konfino viewed the use of phenol to be part of a best way of making copolymer-1. Mylan has thus failed to show that Konfino subjectively viewed the use of phenol to be part of a best mode. See Minco, Inc., 95 F.3d at 1116; see also Shearing, 975 F.2d at 1546. Unable to establish the requisite first prong, Mylan's best mode defense fails. See Young Dental Mfg. Co. v. Q3 Special Prods., Inc., 112 F.3d 1137, 1144 (Fed. Cir. 1997) (explaining that "one proceeds to the second inquiry" " [i]f the inventor had a best mode of practicing the claimed invention"). Even assuming examination of the second prong were necessary, which it is not, Mylan fails to demonstrate that the disclosure of phenol would have been required in order to satisfy the best mode requirement. Since phenol was both widely used in peptide chemistry at the time of the patent application and was a known scavenger of free bromine, its use was both a "true" and "routine" manufacturing detail that did not need to be disclosed in the patents to comply with the best mode requirement. See, e.g., Young Dental Mfg. Co., 112 F.3d at 1144.

v. The Patents' Lack of Disclosure Regarding a "Low Bromotyrosine" Content of Copolymer-1 Is Not a Best Mode Violation

Mylan's other best mode argument—that the patents should have disclosed a "low bromotyrosine" content for copolymer-1—also fails. Mylan offered no direct evidence from Konfino supportive of this claim. Indeed, Konfino was never questioned about the bromotyrosine content of copolymer-1 during his deposition. (PTX 3567 (Konfino Dep.).) The only evidence offered at trial from which any inference concerning Konfino's subjective beliefs could be drawn suggests that bromotyrosine was not important to him. In 1991, Mr. Konfino reported that bromotyrosine was "non-toxic" and Dr. Kent acknowledged this fact at trial. (Sept. Tr. (Kent) 668:22-669:10; PTX 708 at TEV000324554.) Mylan has thus failed to satisfy the subjective prong of the best mode defense. See Minco, Inc., 95 F.3d at 1116; Shearing, 975 F.2d at 1546.

Furthermore, producing copolymer-1 with lower bromotyrosine levels also amounts to a "true" and "routine" manufacturing detail that need not be disclosed to comply with the best mode requirement. The evidence demonstrates that bromotyrosine is an impurity in copolymer-1 and it is standard practice in the pharmaceutical industry to reduce the amounts of impurities in a pharmaceutical product like copolymer-1. (Sept. Tr. (Kent) 773:3-14; Sept. Tr. (Owens) 633:7-12; Sept. Tr. (Gokel) 1597:18-23.) In addition, as explained above, reducing bromotyrosine would have been "routine" given that phenol was a

widely used reagent at the time and known to be capable of reducing free bromine in HBr/acetic acid. (Sept. Tr. (Gokel) 1591:11-1592:13; PTX 961 (Kota Dep. Tr.) at 130:18-131:18.) Accordingly, reducing amounts of a bromotyrosine impurity would have been both a "true" and "routine" production detail at the time of the patent application and did not need to be disclosed to comply with the best mode requirement. See, e.g, Young Dental Mfg. Co., 112 F.3d at 1144.

B. Inequitable Conduct

Defendants allege Dr. Pinchasi committed inequitable conduct by: (1) intentionally deceiving the PTO to believe there was a clear relationship between molecular weight and toxicity; (2) not informing the PTO of her alleged reservations about the RBL test; and (3) intentionally deceiving the PTO by describing a relationship between the RBL test and human side effects that had not been observed. For the reasons set forth below, Defendants fail to prove inequitable conduct by clear and convincing evidence.

i. General Principles

To prevail on the defense of inequitable conduct, the accused infringer must prove that the applicant misrepresented or omitted material information with the specific intent to deceive the PTO." Therasense, Inc. v. Becton, Dickinson & Co. , 649 F.3d 1276, 1287 (Fed. Cir. 2011) (en banc) (citation omitted). Defendants "must prove both elements—intent and materiality—by clear and convincing evidence." Id.

(citation omitted). If Defendants prove both elements, the Court "must weigh the equities to determine whether the applicant's conduct before the PTO warrants rendering the entire patent unenforceable." Id. (citation omitted).

In Therasense, Inc., the Federal Circuit explained that "[i]ntent and materiality are separate requirements" and that courts "should not use a 'sliding scale,' where a weak showing of intent may be found sufficient based on a strong showing of materiality, and vice versa." Id. at 1290 (citation omitted). With respect to the first requirement—specific intent to deceive the PTO—in cases "'involving nondisclosure of information, clear and convincing evidence must show that the applicant made a deliberate decision to withhold a known material reference.'" Id. (citation omitted). "In other words," the Federal Circuit explained in Therasense, Inc., "the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." Id. In view of the fact that "direct evidence of deceptive intent is rare," the Federal Circuit added, "a district court may infer intent from indirect and circumstantial evidence." Id. (citation omitted). "[T]o meet the clear and convincing evidence standard," however, "the specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence.'" Id. (citation omitted).

With respect to the second prong—materiality—in Therasense, Inc., the Federal Circuit explained that "the materiality required to establish inequitable

conduct is but-for materiality." Id. at 1291. "[I]n assessing the materiality of a withheld reference, the court must determine whether the PTO would have allowed the claim if it had been aware of the undisclosed reference." Id. In making this determination, courts "should apply the preponderance of the evidence standard and give claims their broadest reasonable construction." Id. at 1291-92 (citation omitted). While but-for materiality must generally be proven "to satisfy the materiality prong of inequitable conduct," the Federal Circuit "recognizes an exception in cases of affirmative egregious misconduct." Id. at 1291-92. "When the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit, the misconduct is material." Id. at 1292 (citations omitted). "Because neither mere nondisclosure of prior art references to the PTO nor failure to mention prior art references in an affidavit constitutes affirmative egregious misconduct, claims of inequitable conduct that are based on such omissions require proof of but-for materiality." Id. at 1292-93.

ii. The Decision to File the '037 Application

The '037 patent application, which all of the patents-in-suit claim priority to (JPO ¶ 79), was drafted in one night by Dr. Pinchasi, Dr. Ilan Schwartz, Dr. Ralph Haber, and Neil Nachshen. (DTX 1393 (Nachshen Dep. 10/13/10) at 21:7-11, 22:3-15; DTX 1389 (Haber Dep. 10/07/10) at 46:1-20; July Tr. (Pinchasi) 116:24-117:11, 203:18-22.) On May 24, 1994, Nachshen, an employee in Teva's

Patent Department, asked Dr. Pinchasi whether she was aware of any publications related to copolymer-1 that were due for publication. (DTX 1393 (Nachshen Dep. 10/13/10) at 11:22-12:4, 20:22-21:7.) Dr. Pinchasi informed Nachshen that she believed a paper was going to be published that same day in the Proceedings of the National Academy of Sciences ("PNAS"). (DTX 1393 (Nachshen Dep. 10/13/10) at 20:22-21:7.)

Nachshen confirmed the publication date with PNAS at approximately 4:00 p.m., Israeli time, on May 24, 1994. (DTX 1393 (Nachshen Dep. 10/13/10) at 21:16-23:13.) At that point, Nachshen told others at Teva that "if they wanted to have a patent position, today was the day they needed to file." (DTX 1393 (Nachshen Dep. 10/13/10) at 19:18-20:14, 28:9-14; DTX 1394 (Nachshen Dep. 10/13/10) at 28:3-6.) At his deposition, Nachshen recalled that Dr. Pinchasi approved filing a patent application. (DTX 1393 (Nachshen Dep. 10/13/10) at 20:15-17.) Although Dr. Pinchasi had never been involved in preparing a patent application before that day (July Tr. (Pinchasi) at 122:24-123:4), given that she was the project manager for the copolymer-1 project at Teva at that time, there is nothing remarkable about the fact that she was involved in the decision to file a patent application on this occasion. (July Tr. (Pinchasi) 11:6-12).

The '037 application was faxed to the United States for filing with the PTO sometime before 4:00 a.m., Israeli time, on May 25, 1994. (DTX 1393 (Nachshen Dep. 10/13/10) at 22:3-13, 41:15-19; 62:11-22.) Nachshen drafted the '037 application with the

assistance of Dr. Pinchasi, Dr. Haber, and Dr. Schwartz, in consultation with attorneys from the New York City and Washington, D.C. offices of Kenyon & Kenyon LLP (DTX 1393 (Nachshen Dep. 10/13/10) at 19:6-13, 20:15-17, 21:7-11, 40:25-41:3, 41:8-12; July Tr. (Pinchasi) 116:9-20, 117:6-11.) Nachshen, who, at the time, had little to no knowledge regarding the subject matter of the patent application, relied upon the others working with him, including Dr. Pinchasi, to provide technical assistance on the subject matter described and claimed in the patent application. (DTX 1393 (Nachshen 10/13/2010 Dep.) at 22:16-23:6, 23:20-24:21, 26:10-23, 26:24-27:19, 28:25-293, 29:7-16, 32:11-32:24, 33:4-6, 34:24-35:19.)

Dr. Pinchasi provided biological data, specifically in vivo and in vitro RBL degranulation toxicity data, for potential use in the application. (July Tr. (Pinchasi) at 117:6-14, 122:4-7.) Although Dr. Pinchasi provided toxicity data for potential use in the application, she testified at trial that she was "not involved" in the selection of any data that actually went into the '037 application. (July Tr. (Pinchasi) at 146:4-5.) Whether she selected any of the data is largely irrelevant, however, because before the '037 application was filed, Dr. Pinchasi reviewed it and confirmed that it accurately reflected what she knew about the biological toxicity profile of copolymer-1, as measured by the in vivo and in vitro RBL toxicity tests. (July Tr. (Pinchasi) at 129:1-17.)

iii. The Relevant Contents of the '037 Application

The '037 application contains the same Example 2 that appears in the patents-in-suit described above. (Compare PTX 1 at 3:20-4:27 with PTX 10 at TEV003009932-35.) As explained above, Example 2 is entitled "Toxicity Analysis." The '037 application stated, first, in relevant part with respect to the in vivo test, that "[t]hree batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 kDa (less than 2.5% copolymer-1 species over 40kDa) and 22 kDa (more than 5% copolymer-1 species over 40kDa) were subjected to" this test. (PTX 10 at TEV003009932.) Because none of the mice in the 7.3 and 8.4 kDa batches died, these batches "were both designated 'non-toxic,' whereas in the batch with the average molecular weight of 22kDa, 3 out of 5 mice had died ... and it was consequently designated 'toxic.'" (PTX 10 at TEV003009933.)

Second, with respect to the in vitro RBL test, the '037 application included a page explaining that the RBL test "was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system." (PTX 10 at TEV003009934.) In support of this representation, the '037 application cited two publications: "E.L. Barsumian, C. Isersky, M.G. Petrino and R.P. Siraganian, Eur. J. Immunol. 11, 317 (1981)" and "R.P Siraganian, Trends in Pharmacological Sciences, October 1983, 432." (PTX 10 at TEV003009934.) The '037 application, like the specification of the patents-in-suit, also stated that "[t]he RBL degranulation test is .. used in order to

screen out those batches of [copolymer-1] which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (PTX 10 at TEV003009934; PTX 1 at 3 :63-67.)

In regard to the RBL test results, the '037 application explains that "[f]our batches of copolymer-1, with average molecular weight between 8,250-14,500 were analyzed for both the % of species with molecular weight over 40 kDa and for degranulation of RBL's." (PTX 10 at TEV003009935.) The results were summarized in the following table:

Average M.W.	% of species with M.W. over 40 kDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

(PTX 10 at TEV003009935.) The '037 application concluded that "when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa." (PTX 10 at TEV003009935.)

Lastly, the '037 application had different claims from the ones that ultimately issued in later applications that resulted in the patents-in-suit. In particular, the '037 application had no claims directed to copolymer-1 with an average molecular weight in any particular range. (July Tr. (Pinchasi) at 131:11-23; PTX 10 at TEV003009937.) The claims in the '037 application were directed to the percent of

species above 40 kilodaltons or the percent of species between 2 and 20 kilodaltons. (PTX 10 at TEV003009937.)

iv. The April 1994 Data Table

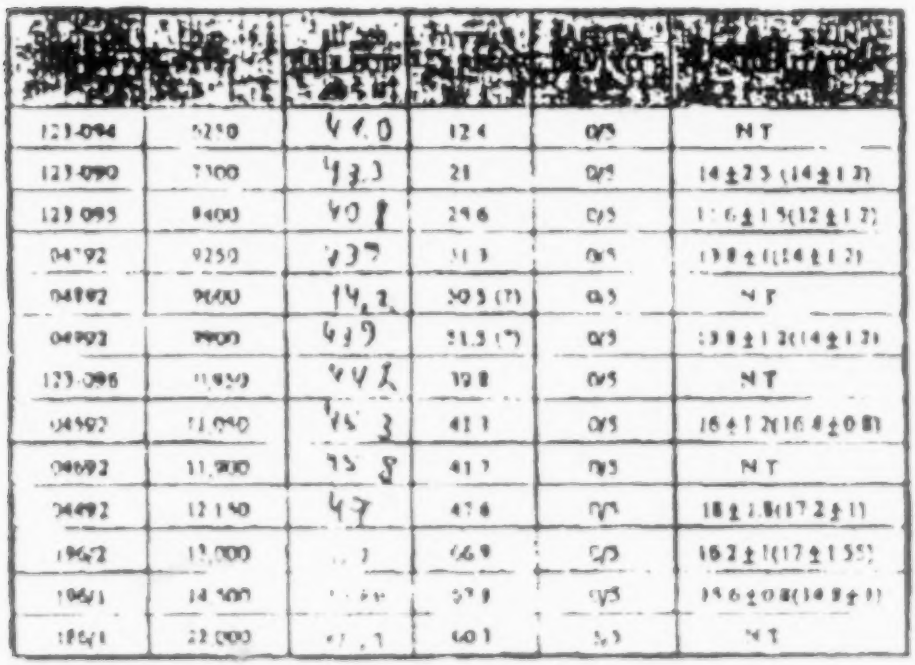
Defendants contend the patents-in-suit were obtained based on the assertion, stemming from Example 2, that copolymer-1 with an average molecular weight below 10 kDa exhibits unexpectedly less toxicity than copolymer-1 in the prior art, including the prior art range of 10 kDa and higher disclosed in the '550 patent. (See PTX 13 at TEV000304142-43 ('808 patent prosecution history, 2/14/97 Office Action citing the '550 patent and acknowledging that the "polymers of the prior art are disclosed to have a specified minimum molecular weight of 10,000" daltons), TEV000304151 ('808 patent prosecution history, 7/14/97 Amendment acknowledging that "the cited reference ['550 patent] teaches a minimum molecular weight of 10 kilodaltons"); see also PTX 14 at TEV00309204; PTX 17 at TEV000304385; PTX 18 at TEV000310451; PTX 19 at TEV000304498; PTX 21.)

Example 2, however, included only a small fraction of Teva's toxicity data. Defendants argue that by providing the PTO with only a sliver of Teva's toxicity data, Dr. Pinchasi intentionally withheld toxicity data from the PTO that undermined the black and white relationship between molecular weight and toxicity described in the '037 application. In support of this argument, Defendants rely heavily on a toxicity data table that Dr. Pinchasi reviewed about a month before the '037 application was filed

("April 1994 Data Table"). (July Tr. (Pinchasi) 123:5-9, 123:17-124:1, 150:2-9 (acknowledging she handwrote the date, April 11, 1994, on the April 1994 Data Table); DTX 999A at TEV001222355-RC; DTX 3149-T (translated version of DTX 999A (at TEV001222355-RC).) Two copies of the April 1994 Data Table were located in Nachshen's patent prosecution files for the patents-in-suit. (DTX 999A at TEV001222355-RC, TEV001222417-RC.)

The April 1994 Data Table contains information for thirteen copolymer-1 batches. (DTX 999A at TEV001222355-RC.) The information includes the average molecular weight for each batch, as well as in vivo and in vitro RBL toxicity data for each batch. (DTX 999A at TEV001222355-RC.) The April 1994 Data Table is shown in Figure 2 3 below: Figure 23

Figure 23



(DTX 999A at TEV001222355-RC.)

The three in vivo mouse assays and four in vitro RBL assays disclosed in Example 2 of the '037 application (and the specification of the patents-in-suit) match data from the April 1994 Data Table exactly. (Compare DTX 999A at TEV1222355-RC with PTX 1 at 3:20-4:27; see also DTX 1391 (Hausdorff Dep. 9/14/10) at 177:12-179:1; DTX 1236 (Declaration of Teva 30(b)(6) witness Sharon Hausdorff, stating that the April 1994 Data Table (TEV001222417) "contain[s] data which appear in the patents").) The chart below, which was created by Mylan, shows, in the shaded boxes, the only data from the April 1994 Data Table that was provided to the PTO:

Batch Number	Average Molecular Weight	Peak III Select	% Release RBL	Safety In vivo	Skin Irritation
123-094	6250	41.0	12.4	0/5	N.T.
123-090	7300	43.3	21	0/5	14 ± 2.5 (14±1.2)
123-095	8400	40.6	25.6	0/5	11.6 ± 1.5 (12±1.2)
04792	9250	43.9	31.3	0/5	13.8 ± 1 (14±1.2)
04892	9600	44.2	50.5 (?)	0/5	N.T.
04992	9900	43.9	51.5 (?)	0/5	13.8 ± 1.2 (14±1.2)
123-096	10,950	44.2	39.8	0/5	N.T.
04592	11,050	45.3	41.3	0/5	[illegible]
04692	11,900	45.8	41.7	0/5	N.T.
04492	12,150	47	47.6	0/5	[illegible]
196/2	13,000	45.7	66.9	0/5	16.2 ± [illegible]
196/1	14,500	44.66	67.8	0/5	15.6 ± 0.8 (14.8±1)
186/1	22,000	47.27	60.3	3/5	N.T.

At trial, Dr. Pinchasi testified that she was not sure whether she personally created the April 1994 Data Table, but that she believes it was one of many summary tables created during the development of

copolymer-1 to compare chemical and biological data related to different batches. (July Tr. (Pinchasi) 124:13-125:1.) She also testified that she may have considered the information in the April 1994 Data Table when she was gathering biological data for the '037 application, but that she had no specific recollection of doing so. (July Tr. (Pinchasi) 125:2-7.) Without any evidence to the contrary and in view of Dr. Pinchasi's demeanor and the fact that she was testifying about a patent application that was filed over seventeen years ago, the Court has no basis for not crediting her testimony regarding her recollection of the April 1994 Data Table.

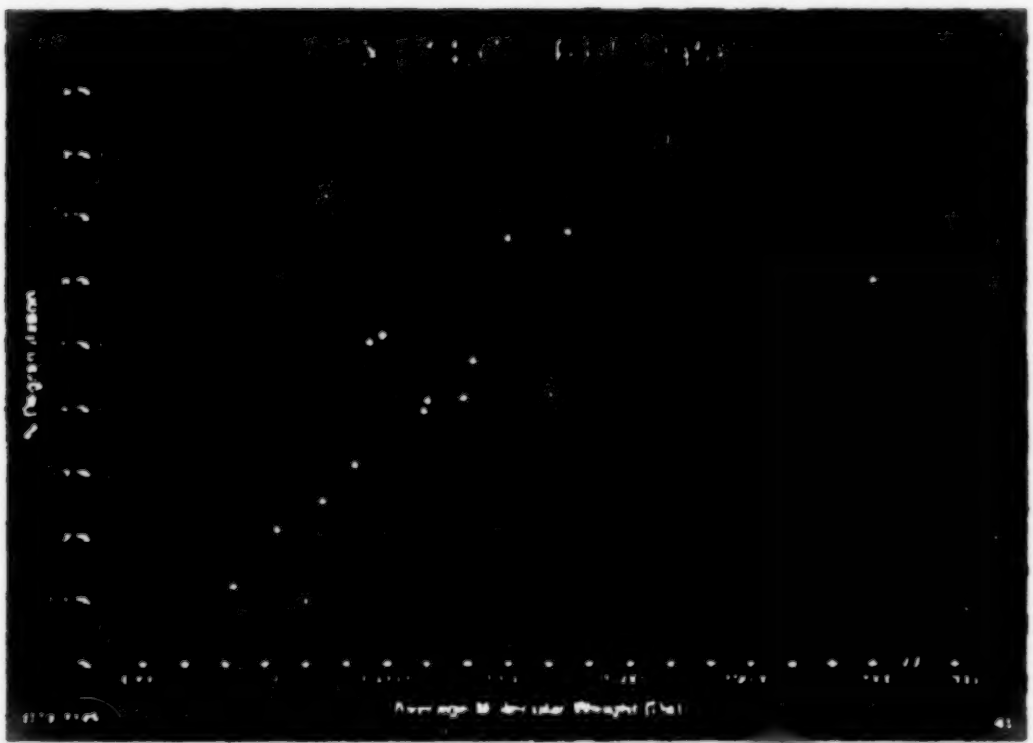
v. The April 1994 Data Table Is Consistent with Example 2

Moreover, contrary to Defendants' argument, the April 1994 Data Table was not inconsistent with the data in Example 2. Example 2 discloses a correlation or trend between molecular weight and toxicity: "when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa." (PTX 1 at 4:25-27; (PTX 10 at TEV003009935; July Tr. (Baird) at 600:3-6 (explaining the converse: "if the percent of high molecular weight species is high, greater than 5 percent, then the percent of release of serotonin, which is indicative of toxicity, is high").)

At trial, Dr. Baird, a recognized expert in the RBL degranulation test, whose testimony the Court credits, took the molecular weight and RBL degranulation data contained in the April 1994 Data Table and plotted them on the graph shown in

Figure 24 below. She found that the data in the April 1994 Data Table show the same trend as seen in Example 2—increasing RBL degranulation with increasing molecular weight. (July Tr. (Baird) 603:7-604:5; PTX 887 at 40.)

Figure 24



Dr. Pinchasi also testified that the data in the April 1994 Data Table "very clearly" shows a correlation: "the higher the average molecular weight, the higher percentage of RBL release." (July Tr. (Pinchasi) 125:14-19.) In fact, even Defendants' expert, Dr. Kimber, conceded (with caveats) that the RBL data in the April 1994 Data Table, like all of the

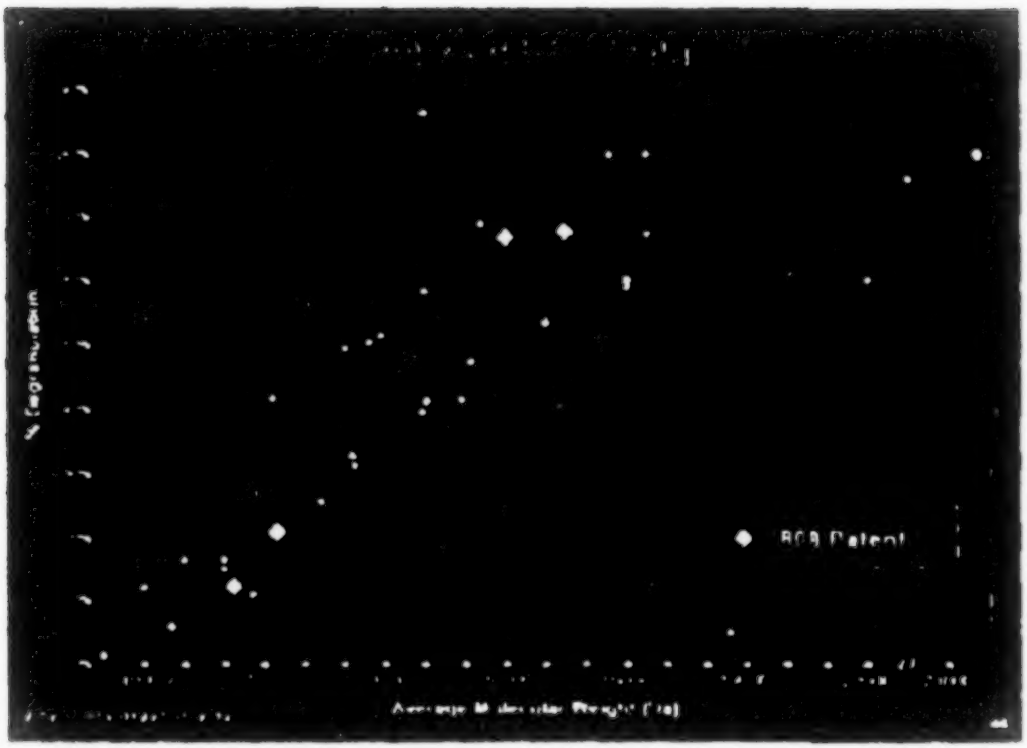
other data he has seen in this case, reflect a trend of increasing RBL degranulation with increasing average molecular weight. (July Tr. (Kimber) 446:22-447:15 (" [W]hat I've seen ... is a correlation, a dot plot, .. between average molecular weight and degree of activity in the RBL assay, with mean values. [I]f you do that, there certainly appears to be a higher likelihood of high levels of degranulation with higher molecular weight compared with lower molecular weight."), 465:2-3, 466:10-19.)

vi. Example 2 Is Representative of Teva's Toxicity Data as a Whole

The Weizmann and Teva scientists performed hundreds of RBL degranulation tests on batches of copolymer-1 while developing the product. (July Tr. (Arnon) 332:8-334:2; PTX 34T; PTX 36T; PTX 53T; PTX 54.) The April 1994 Data Table contains only a small fraction of those test results. The evidence at trial showed that the data in Example 2 was a fair and accurate representation of the data generated by the Teva and Weizmann scientists as a whole. (July Tr. (Arnon) 332:8-334:2; July Tr. (Pinchasi) 30:14-20, 80:13-81:13; July Tr. (Baird) 601:13-24; PTX 887 at 44.)

To demonstrate this, Dr. Baird took molecular weight and RBL degranulation data for several different batches of copolymer-1 found in Teva's internal files that had been cited by Defendants' experts and added them to the graph she created for the data in the April 1994 Data Table. The results are shown below in Figure 25:

Figure 25



The Court agrees with Dr. Baird that the data, again, showed "a very clear trend" consistent with the trend shown in Example 2. (July Tr. (Baird) 601:13-24, 605:14-18; PTX 887 at 44.)

Teva and Weizmann's in vivo toxicity data is also consistent with Example 2, and Defendants provided no expert testimony to the contrary. Although the only copolymer-1 batch in the April 1994 Data Table that failed the in vivo toxicity test had a molecular weight of 22,000 daltons, Teva and Weizmann had internal data on many batches of copolymer-1 with molecular weights between 10,000 and 22,000 daltons that had failed that test. (July Tr. (Pinchasi) 126:4-8; PTX 34-T.)

Further, Defendants did not provide their expert Dr. Kimber with all of the RBL degranulation and in vivo mouse test data that had been produced by Teva in this case. (July Tr. (Kimber) 426:21-429:16, 438:13-439:1.) Accordingly, Dr. Kimber did not know whether the data in the April 1994 Data Table reflected the universe of toxicity data that had been generated by Weizmann and Teva, and could not provide an opinion on whether Teva's data as a whole was consistent with Example 2. (July Tr. (Kimber) 438:18-439:5.)

vii. The Patent Office Was Aware That Not All High Molecular Weight Copolymer-1 Batches Were Toxic

Contrary to Defendants' argument, Example 2 does not represent that all batches of copolymer-1 above 10 kDa were toxic. First, Example 2 does not explicitly state that all batches above 10 kDa were toxic and that all batches below were not. (PTX 1 at 3:20-4:27; PTX 10 at TEV003009932-35.) Second, to the extent Defendants attempt to read such a statement into Example 2 by emphasizing that Dr. Pinchasi did not disclose that Teva possessed toxicity data for additional batches of copolymer-1, Example 2 explicitly rejects such an interpretation: "when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity is low, and vice versa." (PTX 1 at 4:25-27; PTX 10 at TEV003009935.) As Dr. Baird explained, this statement indicates a trend in the data, not any hard cut-off. (July Tr. (Baird) 600 : 7-14.)

Moreover, Dr. Bornstein's 1987 article, cited in the specification of the patents-in-suit (and in the (037 application), explicitly states that some batches of copolymer-1 with a molecular weight between 14,000 and 23,000 daltons showed less than 30% degranulation in the RBL assay—i.e., they were "non-toxic."[18] (PTX 1 at 1:25-28; PTX 11 at TEV000309437; PTX 31 at 408-09.) The file histories indicate that the PTO examiner reviewed and considered the Bornstein article during the prosecution of the patents-in-suit. (PTX 18 (File History of U.S. Patent No. 6,362,161 ("'161 File History")) at TEV000310385-89; PTX 14 (File History of U.S. Patent No. 5,981,589 ("'589 File History")) at TEV000309018-21; PTX 21 (File History of U.S. Patent No. 7,199,098 ("'098 File History")) at TEV000308838-842.)

In view of the specification and the prosecution, the Court finds that the PTO was aware that not all higher molecular weight copolymer-1 batches were toxic.

viii. Dr. Pinchasi's Views on the RBL Degranulation Test

In a December 1989 memo, Dr. Pinchasi set forth her rationale for adopting a second screening test, the in vivo toxicity test, in addition to the RBL degranulation test. (DTX 3385.) Defendants point to

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[18] As explained earlier, Weizmann scientists adopted the RBL degranulation test to test toxicity, and designated as "toxic" and discarded batches that released 30% or more serotonin upon exposure to copolymer-1. (July Tr. (Arnon) 327:8-330:18; PTX 31 at 409.)

this memo as evidence that Dr. Pinchasi knew the RBL test was unreliable, not reproducible, and could not be used as a toxicity screen.

As an initial matter, Defendants are correct that the December 1989 memo criticized the RBL test. The memo notes "that the RBL system is inconsistent in its reproducibility, and both inter-assay and intra-assay large variations were observed." (DTX 3385 at TEV001222393.) It also notes that "many times we see that a whole experiment is skewed, either upward or downward, without our controls detecting it" and concludes that "we thus feel that this assay cannot be properly controlled." (DTX 3385 at TEV001222394.) Although the RBL test was "very convenient for the screening of many batches at a time," because of its shortcomings, "the RBL system is not sufficiently reproducible so as to afford the ultimate analysis for the safety of our batches." (DTX 3385 at TEV001222392.) Because the in vivo test was "dependable" and "found to be almost totally reproducible[,]" (DTX 3385 at TEV001222393), it was adopted to complement the RBL test. (July Tr. (Pinchasi) at 29: 1-19.)[19]

At trial, Dr. Pinchasi testified that the RBL test was "very good" for screening "toxic batches during

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[19] Defendants also emphasize the fact that the memo criticized "upper permitted level of RBL degranulation (40%)" inherited from the Weizmann Institute as "arbitrar[y.]" (DTX 999A at TEV001222392-RC.) They also highlight that the memo suggested adopting a 50% cutoff, which the memo deemed "non-arbitrary and meaningful." (DTX 999A at TEV001222393-RC.)

process development and preparation." (July Tr. (Pinchasi) at 103:10-13.) "[B]ecause of its relatively high variation," Dr. Pinchasi added, Teva decided the RBL test was not "sufficiently reproducible to [serve] as a sole, as a single, an only methodology to be used to decide whether a batch is safe for clinical use or not." (July Tr. (Pinchasi) at 103:13-16.) Accordingly, Dr. Pinchasi explained, Teva concluded it "needed another complementary test." (July Tr. (Pinchasi) at 103:16-17.)

Despite the reservations discussed above, the evidence shows Teva continued to use the RBL test after the December 1989 memo, in conjunction with the in vivo test, until at least December 1992. (PTX 723; PTX 62.) Thus, the Court finds, even though Dr. Pinchasi (and Teva) believed the RBL test had reliability and reproducibility issues, that did not stop them from continuing to use it as a toxicity screen.

ix. Professor Arnon Believed the RBL Degranulation Test To Be a Reliable Screening Test for Toxicity

The evidence at trial also established that Dr. Pinchasi did not select the RBL degranulation test. One of the other inventors of the patents-in-suit, Professor Arnon, selected the test after concluding that it was an appropriate assay for screening batches of copolymer-1 for toxicity. Even after Teva took on development of copolymer-1, the RBL testing continued to be performed at the Weizmann Institute. (July Tr. (Pinchasi) 30:7-20; July Tr. (Arnon) 332:8-25; July Tr. (Baird) 608:25-609:10.)

Before adopting the RBL degranulation test, Professor Arnon personally read all of the literature about the test, including articles by Dr. Reuben Siraganian's group at NIH, who were the leading experts on the test. (July Tr. (Arnon) 321:19-25.) One of the literature references Professor Arnon considered was the 1981 Barsumian article referenced above. Dr. Barsumian was a member of the Siraganian group at NIH. The Barsumian article reported that the RBL degranulation test had a reproducibility of approximately 20%. (July Tr. (Arnon) 325:14-326:1; PTX 522 at 320.) Given this data, Dr. Barsumian concluded that the test was "quite reproducible." (July Tr. (Arnon) 321:19-326:13, 337:7-16; PTX 522 at 322.) Based on the literature available at the time and Professor Arnon's experience with biological assays, she and her colleagues at the Weizmann Institute determined that the RBL degranulation test, with its approximately 20% reproducibility, was "quite reliable." (July Tr. (Arnon) 321:8-326:25, 336:2-337:17; PTX 522; PTX 711; DTX 3114.)

Teva and Weizmann's protocol for performing the RBL degranulation test was contained in a specification drafted by Weizmann scientist Dr. Teitelbaum, not Dr. Pinchasi. Professor Arnon reviewed the RBL specification. (July Tr. (Pinchasi) 89:23-91:4; July Tr. (Arnon) 334:14-23; DTX 3114.) The RBL specification was later signed and approved by Dr. Pinchasi. (July Tr. (Pinchasi) 89:23-91:4; DTX 3114.) According to the RBL specification drafted by Dr. Teitelbaum, the RBL degranulation test was used "to screen out those batches of cop-1 which evoke substantial degranulation and thus might

elicit undesirable local and/or systemic side effects." (DTX 3114 at TEV000881362.) As indicated above, this exact statement was included in the '037 application and the specification of the patents-in-suit. (PTX 10 at TEV003009934; PTX 1 at 3:63-67.) At trial, Professor Arnon testified that, to this day, she believes this is an accurate statement of the appropriate use of the RBL degranulation test. (July Tr. (Arnon) 334:24-335:14.)

The RBL specification shows that the test was validated, meaning that it was proven to be precise and reproducible enough for the purposes for which it was being used. (July Tr. (Pinchasi) 92:22-93:17; DTX 3114 at TEV000881368.) The precision of the RBL degranulation test (in terms of its relative standard deviation ("RSD")) was reported as ± 19%, and its reproducibility (in terms of RSD) was reported as ± 26%. (July Tr. (Pinchasi) 94:9-15; DTX 3114 at TEV000881368-69.) Professor Arnon testified that this level of precision and reproducibility was both acceptable and within the range of what the Weizmann scientists expected. (July Tr. (Arnon) 336:2337: 6.)

x. The RBL Degranulation Test Described in the Patent Is a Well-Accepted Test in the Scientific Community

At trial, Dr. Baird testified that the RBL degranulation test is a very reliable and reproducible test that is widely used by the scientific community as a model for immediate hypersensitivity that might occur in humans. (July Tr. (Baird) 585:9-21, 595:4-

16, 596:25-597:8, 610:6-20, 611:15-22; PTX 522.) In particular, she agreed with the description of the RBL test set out in the patent, and believes it was reasonable for the Weizmann Institute and Teva scientists to use the test for the purpose described in the patents-in-suit (and the '037 application)—"to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects." (July Tr. (Baird) 593:21-597:8.) As explained above, this language was taken directly from the RBL specification written by the scientists at the Weizmann Institute. (July Tr. (Pinchasi) 286:11-288:16; PTX 1 at 3:63-67; PTX 10 at TEV003009934; DTX 3114 at TEV000811362.)

The Court also takes note of the fact that Defendants themselves have performed RBL degranulation testing and have acknowledged its acceptance in the scientific community. Dr. Rao, Defendant Natco's President of Research and Development, testified that Natco performed RBL degranulation testing, and that the RBL degranulation test is a "well-known toxicity test for hypersensitivity reactions to products" that is "predictive of hypersensitivity in humans." (PTX 883 (Rao Dep.) at 149:22-150:4.) Defendant Momenta developed an RBL test similar to the one used by Teva and described in the patents-in-suit. Momenta found the precision of its test to be ±35%, substantially lower than Teva's. It nevertheless concluded, and then represented to the FDA, that its RBL degranulation test was reproducible. (July Tr. (Kimber) 451:23-460:17; PTX 230 at MMT00927146; PTX 349 at SDZ0018127-34.)

Although Dr. Kimber, Defendants' expert, testified that the RBL degranulation test is not sufficiently reproducible to draw any conclusions about the toxicity of copolymer-1, he has limited experience with the test, and has never performed the test himself. (July Tr. (Kimber) 426:1-3, 426:8-17.) His testimony was based entirely on the variability for the test described in the RBL specification. Moreover, at trial, he conceded that the reproducibility of Teva's RBL degranulation test was actually better than both the reproducibility reported in the Barsumian paper and the reproducibility found by Momenta. (July Tr. (Kimber) 449:13-451:9; 458:25-460:17.) For these reasons, the Court does not credit Dr. Kimber's testimony regarding the RBL test.

Lastly, the Court notes that the Bornstein article, which was peer-reviewed, explicitly describes use of the RBL degranulation test as a toxicity screen for copolymer-1 batches. The fact that the article was peer-reviewed constitutes additional evidence that the RBL test was generally accepted by the scientific community. (July Tr. (Arnon) 329:3-331:4; PTX 31 at 409.)

xi. The Patent Office Knew About the Reproducibility of the RBL Degranulation Test

Example 2 of the '037 application and the patents-in-suit cites the same two literature references cited in the RBL specification: the Barsumian and Siraganian articles. The Barsumian article specifically reported a reproducibility of ± 20% for

the RBL degranulation test. (PTX 1 at 3:50-55; PTX 522.) Thus, the examiner was aware of the reproducibility of the test when making the decision to allow the claims to issue.

In light of these findings of fact, the Court makes the following conclusions of law with respect to Defendants' claim of inequitable conduct.

xii. The April 1994 Data Table and the RBL Degranulation Information Were Not Material

Defendants assert that Dr. Pinchasi's withholding of toxicity data and her concerns about the RBL test from the PTO constitute "affirmative acts of egregious misconduct." In Therasense, Inc., the Federal Circuit was clear, however, that "neither mere nondisclosure of prior art references to the PTO nor failure to mention prior art references ... constitutes affirmative egregious misconduct." 649 F.3d at 1292-93. Omissions, such as the ones alleged here, "require proof of but-for materiality." Id. at 12 93. To prove materiality under the "but-for" standard, Defendants had to prove "the PTO would not have allowed a claim had it been aware" of the April 1994 Data Table or Dr. Pinchasi's views on the RBL degranulation test. See Id. at 1291.

Defendants have failed to establish materiality under that standard. First, with respect to the April 1994 Data Table, the Court concludes that the trend reflected in that Table was evidenced by the other information that was before the PTO and was, therefore, cumulative. For example, as discussed

above, Example 2 was representative of (and consistent with) all of Teva's toxicity data, including the April 1994 Data Table (July Tr. (Arnon) 332:8-334:2; July Tr. (Baird) at 600:3-6, 601:12-24, 603:7-604:5, 605:14-18; July Tr. (Pinchasi) 30:14-20, 80:13-81:13, 125:14-19, 126:4-8; July Tr. (Kimber) 446:22-447:15, 465:2-3, 466:10-19; PTX 34-T; PTX 887 at 40, 44; supra Fig. 26; supra Fig. 27.)

As such, the April 1994 Data Table was not material. See Star Scientific, Inc. v. R.J. Reynolds Tobacco Co., 537 F.3d 1357, 1367 (Fed. Cir. 2008) ("It is well-established ... that information is not material if it is cumulative of other information disclosed to the PTO.") (citations omitted); Honeywell Int'l Inc. v. Universal Avionics Sys. Corp., 488 F.3d 982, 1000 (Fed. Cir. 2007) ("Information cumulative of other information already before the Patent Office is not material.").

Second, with respect to Dr. Pinchasi's views regarding the RBL test, the evidence at trial established that Teva continued to use the RBL test even after the December 1989 memo that was critical of the RBL test. (PTX 723; PTX 62.) Moreover, to the extent Dr. Pinchasi had reservations about the RBL test, the evidence at trial established that Dr. Arnon, whose testimony the Court credits, viewed (and continues to view) the test as reliable and reproducible enough to screen batches of copolymer-1 for toxicity. (July Tr. (Arnon) at 320:7-321:18, 321:8-326:25, 327:22-331:4, 336:2-337:17.) The evidence also showed that the scientific community, including literature that was explicitly cited in the '037 application and the specification of the patents-in-

suit, recognized the test as a reliable and reproducible model for examining immediate hypersensitivity that might occur in humans. (July Tr. (Baird) 585:9-21, 593:21-597:8, 595:4-16, 596:25-597:8, 610:6-20, 611:15-22; July Tr. (Kimber) 451:23-460:17; PTX 31 at 409; PTX 230 at MMT00927146; PTX 349 at SDZ0018127-34; PTX 522; PTX 711; PTX 883 (Rao Dep.) at 149:22-150:4; DTX 3114 at TEV000811362.) In view of these facts, Defendants have failed to show that "the PTO would not have allowed a claim had it been aware" of Dr. Pinchasi's concerns about the RBL degranulation test. See Therasense, Inc., 649 F.3d at 1291.

xiii. Defendants Failed to Establish that Dr. Pinchasi Intended to Deceive the PTO

Even if Defendants had established materiality, which they did not, they failed to establish by clear and convincing evidence that Dr. Pinchasi intended to deceive the PTO. As an initial matter, Defendants proffered no direct evidence that Dr. Pinchasi intended to deceive the PTO. With respect to indirect and circumstantial evidence, under Therasense, Inc., "specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence.'" 649 F.3d at 1290 (citation omitted). Such an inference cannot be drawn here.

First, in regard to the toxicity data, it is irrelevant whether Dr. Pinchasi personally selected the in vivo and in vitro RBL test batches that were included in the '037 application. The crucial facts are that she reviewed the '037 application before it was filed and

confirmed that it accurately reflected what she knew about the biological toxicity profile of copolymer-1, as measured by the in vivo and in vitro RBL toxicity test. (July Tr. (Pinchasi) at 129:1-17.) Because the evidence at trial established that there was a clear trend between increasing RBL degranulation and increasing average molecular weight, "specific intent to deceive" is not "'the single most reasonable inference'" to draw "'from the evidence.'" Therasense, Inc., 649 F.3d at 1290 (citation omitted).

Second, in regard to her concerns regarding the RBL degranulation test, while the RBL degranulation test was not able "to afford the ultimate analysis for the safety of [Teva's] batches[,]" (DTX 3385 at TEV001222392), used in conjunction with the in vivo test, the two tests were "complementary from the point of view of how they can predict clinical safety." (July Tr. (Pinchasi) at 29:18-19.) In view of the fact that Teva continued to use the RBL degranulation test after Dr. Pinchasi's December 1989 memo that was critical of the RBL test (PTX 723; PTX 62), "specific intent to deceive" is not "'the single most reasonable inference'" to draw from the withholding of Dr. Pinchasi's concerns about the RBL degranulation test from the PTO. Therasense, Inc., 649 F.3d at 1290 (citation omitted).

For the reasons provided above, Defendants failed to establish inequitable conduct by clear and convincing evidence.

C. Lack of Enablement

With Sandoz taking the lead, Defendants argue that the patents-in-suit are invalid for lack of enablement. According to Sandoz, in 1994, a person of ordinary skill in the art would not have been able to make copolymer-1 with the claimed molecular weights without undue experimentation because the patents-in-suit do not identify the standards that should be used to calibrate the SEC column.

i. General Principles

Section 112 of the Patent Act provides, in pertinent part, "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains ... to make and use the same." 35 U.S.C. § 112, ¶ 1. "The test of enablement is whether" a person of ordinary skill in the art "could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." U.S. v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988) (citation omitted); see also Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1253 (Fed. Cir. 2004) (explaining that a patent claim is invalid for lack of enablement "only if one skilled in the art, after reading [it], could [not] practice the invention claimed ... without undue experimentation") (citation omitted).

Determining "what constitutes undue experimentation in a given case requires the

application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988) (citation omitted). In Chiron Corp., the Federal Circuit explained that "[t]he fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive." 363 F.3d at 1253 (citations and internal quotation marks omitted). Indeed, "'a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996) (citation omitted).

In In re Wands, the Federal Circuit explained that " [f]actors to be considered in determining whether a disclosure would require undue experimentation" include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

858 F.2d at 737 (citation omitted).

A "person of ordinary skill ... is presumed to be aware of all the pertinent prior art." Custom

Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962 (Fed. Cir. 1986) (citation omitted). As a result, "'[a] patent need not teach, and preferably omits, what is well known in the art.'" Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (alteration in original) (citation omitted).

Lack of enablement must be proven by clear and convincing evidence, see Microsoft Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2242 (2011), as of the filing date of the patent application, see Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1345 (Fed. Cir. 2000).

ii. A Person of Ordinary Skill

The testimony of the experts at trial established that the relevant level of skill in the art was high. And although not all of the experts stated as much, the Court finds that, in 1994, a person of ordinary skill in the art would have had experience and skills in SEC. (Sept. Tr. (Grant) 189:22-190:6; PTX 986 at 3 (an "advanced degree or equivalent in a chemical or biological discipline, and significant experience in the synthesis or characterization of polymers, including proteins or synthetic peptides"); Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9 ("a Ph.D. in chemistry, biochemistry or related field with a minimum of three years of experience in chromatography and specifically in size exclusion chromatography of macromolecules"); Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4 ("extensive experience in the synthesis, fractionation, and characterization of polymers, such as their hydrodynamic and structural properties, as applied to proteins, synthetic peptides

and/or polydisperse peptide mixtures, as well as experience in the determination of the molecular weight distribution and average molecular weights of such polymers by methods such as size exclusion chromatography (SEC), and an understanding of how the standards and conditions used in the molecular weight determination affect the results obtained.")

iii. Self-Standards

As explained above, the specification expressly describes use of a calibrated SEC column.[20] (PTX 1 at 3:6-8.) At trial, Dr. Grant testified that, in 1994, there were two ways a person of ordinary skill in the art could accurately measure the molecular weight of copolymer-1: self-standards and universal calibration. In 1994, a person of ordinary skill in the art would have known that to accurately correlate the retention time of the molecules coming out of an SEC column with their molecular weights, the column must be calibrated using standards with the same hydrodynamic characteristics as the sample being measured. (Sept. Tr. (Grant) 1412:6-1413:16; Sept. Tr. (Scandella) 1314:15-1316:24; PTX 961 (Kota Dep.) 18:3-14; PTX 962 (B. Rao Dep.) at 75:6-76:10, 78:14-80:5; PTX 973 (Venkataraman Dep.) at 108:20-109:23; PTX 974 (Wallingford Dep.) 146:9-149:7; PTX 317 at MYL0000111; PTX 553 at 72.) Because self-

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[20] Defendants emphasize a July 4, 1996 Teva document that states, "[I]t should be explicitly stated by which analytical method the molecular weight data were obtained." (DTX 31317 at TEV000290820.) As Dr. Grant testified(however, that is precisely what the patents-in-suit do: "They explicitly state that you should use size exclusion chromatography." (Sept. Tr. (Grant) 325:17-18.)

standards are made from the same material as the sample being measured, by definition, they have the same hydrodynamic volume-to-molecular weight characteristics as the sample being measured. (Sept. Tr. (Grant) 1399:23-1400:13.) As a result, the shape of copolymer-1 has no bearing on the use of self-standards.

By 1994, self-standard calibration had been thoroughly described in the scientific literature. For example, Billingham 1977 states that "[t]he most obvious method is to inject into the columns a series of monodisperse standards of the polymer under test" and that "[d]irect calibration with the polymer under test can be achieved by using narrow distribution fractions of the polymer." (PTX 514 at 210-11; Sept. Tr. (Grant) 1414:8-1415:17.)

Self-standards can be obtained two ways. The first is to use whole batches of the polymer of interest having different molecular weights ("whole polymer" self-standards). The second is to use narrower fractions of the polymer sample of interest ("fractionated" self-standards). (Sept. Tr. (Grant) 1399:23-1400: 13.)

The first method, whole polymer self-standards, involves taking whole batches of the polymer of interest, each batch having a different molecular weight, and determining the molecular weights of the batches by independent (non-SEC) methods. (Sept. Tr. (Grant) 1401:9-11, 1418:7-15.) The whole polymer self-standard method was described in the literature well before 1994. (Sept. Tr. (Grant) 1401:9-11; 1418:7-1420:20; PTX 514 at 211; PTX 566 at 37.)

Billingham 1977, for example, describes two different methods of calibration using whole polymer standards in a section entitled "Calibration with Whole Polymer." (PTX 514 at 212-13; Sept. Tr. (Grant) 1401:9-11.) Similar methods are also described in Barth 1991, which includes two sections entitled "Calibration Using Polydisperse Standards of Known Molecular Weight Averages" and "Calibration Using Standards of Known Molecular Weight Distribution." (Sept. Tr. (Grant) 1419:13-1421:3; PTX 566 at 37-44.)

In 1994, a person of ordinary skill in the art could have made whole batches of copolymer-1 to use as self-standards because the patents-in-suit teach how to make copolymer-1 of varying molecular weights. These batches could then be used as molecular weight standards. (PTX 1, col. 4:59-65; Sept. Tr. (Grant) 1401:19-1402:4; DTX 4022 (Varkony Dep.) at 252:4-13, 252:25-253:6, 257:17-22.) At trial, Dr. Sampson explained that by varying the time and temperature of the HBr/acetic acid reaction step in the synthesis of copolymer-1, the molecular weight of the resulting copolymer-1 can be controlled. (Sept. Tr. (Sampson) 1641:6-1642:8; PTX 992 at 6-7.)

With respect to the second method, the fractionated self-standard method involves taking a mixture of the substance of interest and separating it into smaller portions, or fractions, that can be used as calibration standards. (Sept. Tr. (Grant) 187:8-14.) The fractionated self-standard method had been fully described in the literature prior to 1994. (Sept. Tr. (Grant) 1400:16-18.) For instance, Billingham 1977 states that "[d]irect calibration with the polymer

under test can be achieved by using narrow distribution fractions of the polymer, prepared either by preparative fractionation or by preparative scale GPC." (Sept. Tr. (Grant) 1414:12-1418:6; PTX 514 at 211-12.)

Moreover, fractionation of copolymer-1 into smaller portions of varying molecular weight is described in the patents-in-suit. The patent describes fractionation of copolymer-1 by running a sample through an SEC column and collecting the fractions as they exit the column. (PTX 1, col. 2:57-3:2; Sept. Tr. (Grant) 1400:16-1401:8, 1402:5-9; Sept. Tr. (Scandella) 1322:20-1324:7.) Each of the resulting fractions will have a different molecular weight, which can be independently measured so that the fractions can be used as calibration standards. (Sept. Tr. (Grant) 1402:10-24.)

Once self-standards are made—whole or fractionated—a person of ordinary skill in the art would have measured their molecular weights by an independent (non-SEC) method.[21] (Sept. Tr. (Grant) 205:6-10, 1402:10-18.) The methods available for measuring the molecular weights of self-standards in 1994 included multi-angle light scattering, viscometry, ultracentrifugation, and mass spectrometry. (Sept. Tr. (Grant) 1402:19-1403:2; Sept. Tr. (Scandella) 1318:2-8.)

Once the molecular weights of the self-standards had been measured, a person of skill in the art would

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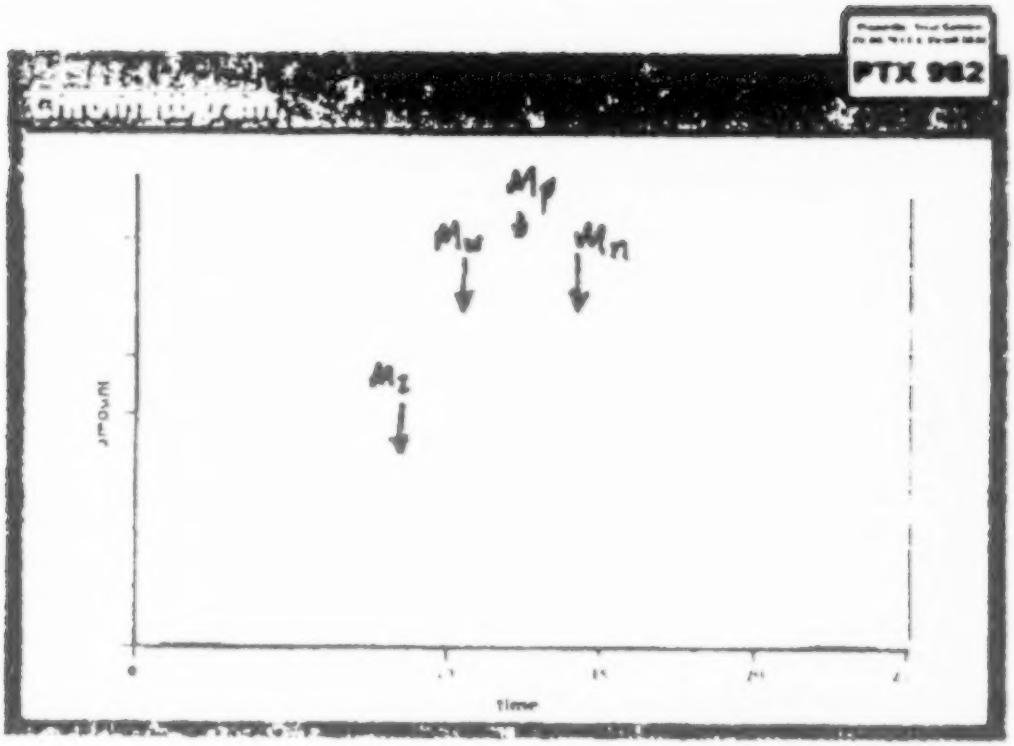
[21] Some of these methods are known as absolute molecular weight methods. (Sept. Tr. (Grant) 1416:14-17.)

use them to calibrate the SEC column by running them through the column, recording the times at which they exit the column, and then creating a calibration plot to correlate their molecular weights to their retention times. (Sept. Tr. (Grant) 1402:10-18.)

If self-standards were used for calibration, however, their average molecular weights could vary depending on the absolute method used to determine the molecular weight of the standard. Light scattering, for example, could measure a weight average molecular weight, while osmometry could measure a number average molecular weight. The different average molecular weight values provided by the various techniques would correspond to different retention times along the chromatogram for the sample. (Sept. Tr. (Grant) 1404:7-20; Sept. Tr. (Scandella) 1326:19-1327:16.) If, for instance, the various molecular weights are mapped out on a chromatogram shaped as in PTX-982, the z-average molecular weight (Mz) would come out first (because it is the highest value and larger molecules exit the size exclusion column first) , then the weight average molecular weight (Mw) , followed by the peak average molecular weight (Mp) at the peak of the chromatogram, and then the number average molecular weight (Mn) after the peak (because it is generally the smallest of the "average" values), as shown below in Figure 26. (PTX 982; Sept. Tr. (Scandella) 1325:2-1326:18; Sept. Tr. (Grant) 1404:23-1405 :13.)

Figure 26



At trial, Dr. Scandella testified that the different average molecular weight values measured by the different absolute measurement methods for the standards would result in different calibration curves, which, in turn, would lead to different determined molecular weights for the sample depending on which calibration was used. (Sept. Tr. (Scandella) 1272:3-25; DTX 3581 at 16.) On cross-examination, he admitted, however, that although each different type of measured average molecular weight for a standard would be associated with a different retention time, the demonstrative he used to show the flaw he alleged, depicted all of the different average molecular weights as being associated with the same retention time. (Sept. Tr. (Scandella) 1326:24-1327:21.)

The Court credits Dr. Grant's explanation regarding why Dr. Scandella's demonstrative was inaccurate. (Sept. Tr. (Grant) 1403:14-1404:20.) Despite the potential difference in the average molecular weight (and hence the corresponding retention time) obtained using different absolute measurement techniques, in 1994, it was well known how to appropriately apply the different measured average molecular weights obtained using different methods to get an appropriate calibration curve that would provide an accurate molecular weight. (Sept. Tr. (Grant) 327:9-16.) The process of obtaining a single accurate calibration curve from the measured molecular weights of self-standards was described extensively in the literature. (Sept. Tr. (Grant) 1403:3-13.) The literature provided numerous examples of procedures that could have been used to resolve calibration curves produced by different absolute molecular weight measurement techniques into a single calibration curve. (Sept. Tr. (Grant) 1408:25-1409:4.)

For fractionated self-standards, for example, Billingham 1977 describes ways to calculate the peak molecular weight of the self-standards such that it can be accurately applied at the peak time. Dr. Grant explained that this means that "since a number average or a weight average is not going to have a time associated with it that's equal to the peak, you have to do some calculation or adjustment to be able to find what the accurate molecular weight is at the peak." (Sept. Tr. (Grant) 1414:22-1417:3; PTX 514 at 211.) Dr. Grant also explained that a paper from the early 1970s cited by Billingham 1977 describes "several different types of methods that had already

been developed by that time to do this adjustment, this calculation of the peak molecular weight from other types of average molecular weights." Dr. Grant explained further that mathematical treatments that could be used to convert number average or weight average molecular weights into peak molecular weights were described in the literature in 1994. (Sept. Tr. (Grant) 1417:4-1418:6; PTX 514 at 211.)

Additionally, Barth 1991 describes a variety of methods for generating calibration curves using polydisperse self-standards. (PTX 566 at 37-41.) Dr. Grant explained that Barth 1991 describes "a process that allows you to determine the accurate molecular weight at the peak for constructing a valid calibration curve" because "Mn and Mw are average molecular weights that can be determined by absolute methods" and "they do not correspond to molecular weights at the same time as the peak." (Sept. Tr. (Grant) 1419:13-1421:3; PTX 566 at 37.)

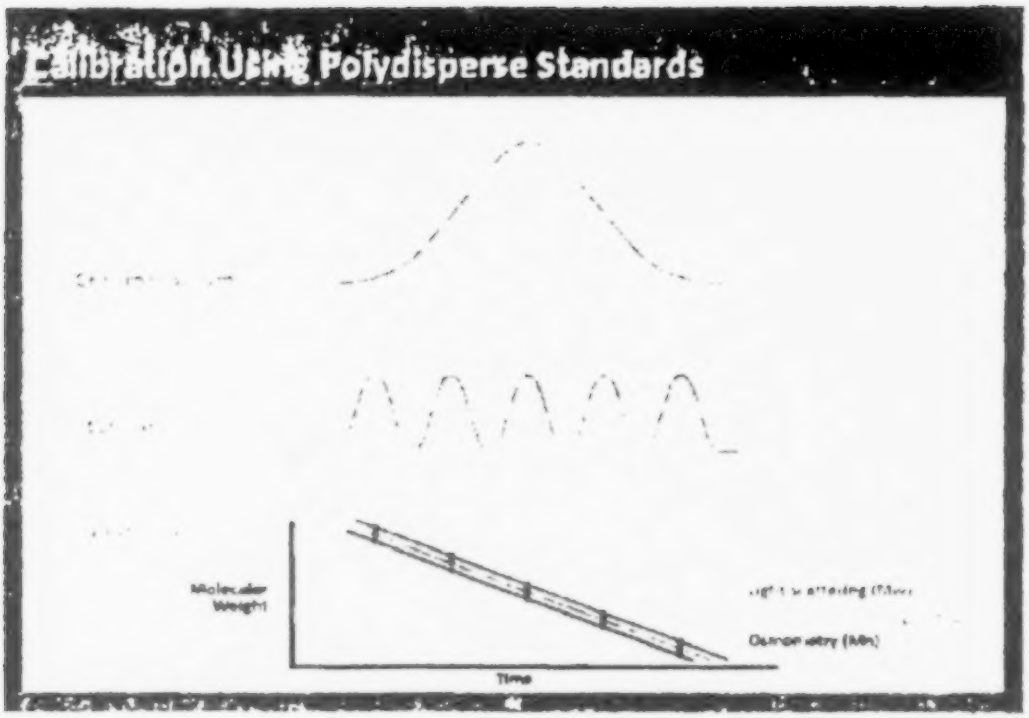
Dr. Grant further explained that Billingham 1977 and Barth 1991 represent only a very small part of the literature that was available in 1994 describing the processes for generating valid calibration curves. He emphasized that "there are well described and valid and effective methods to take calibration curves that may be constructed from different types of average molecular weights and resolve them into a single calibration curve, so that . . in the end you only ha[ve] [a] single valid calibration curve, [which] gives you an accurate molecular weight at the peak of your measuring." (Sept. Tr. (Grant) 1421 :4-18.)

At trial, Dr. Grant presented a demonstrative to explain how a person of ordinary skill in the art would apply different average molecular weight results from different techniques to generate a single valid calibration curve. (Sept. Tr. (Grant) 1406:1-1409:11; PTX 990 at 4a-i.) Dr. Grant presented an illustrative chromatogram of five broad self-standards, such as copolymer-1 self-standards, and a calibration curve based on the peak molecular weight times of the self-standards. (Sept. Tr. (Grant) 1406:1-17; PTX 990 at 4a.)

Dr. Grant explained that one would get different calibration curves if the different average molecular weights for the standards obtained through different absolute molecular weight measurement techniques were assigned to the same retention time. This occurs because, as shown in his example, one technique, light scattering, gives a higher average value (a

"weight" average (Mw)) than the peak average value, while a second technique, osmometry, gives a lower average value (a "number" average (Mn)) than the peak average value, but the weight average and number average values are erroneously being applied at the same time (the "peak" time). (Sept. Tr. (Grant) 1406:18-25,1407:7-13; PTX 990 at 4c.)

Figure 27



Dr. Grant explained that an adjustment was described extensively in the pre-1994 literature that addressed this issue. This adjustment would allow the different average molecular weights to be applied at the correct time. Such an adjustment—calculating the molecular weight of the standard at the peak so that it could be accurately applied at the peak time or appropriately applying the measured average molecular weight of the standard at its appropriate time—would cause the theoretically different calibration curves to be merged into a single accurate calibration curve. (Sept. Tr. (Grant) 1406:25-1407:6; PTX 990 at 4c-i.)

Dr. Grant also demonstrated how a calibration curve based on weight average molecular weight (which is a larger value than the peak molecular

weight value and therefore corresponds to a time to the left of the peak) of self-standards could be adjusted. (Sept. Tr. (Grant) 1407:20-1408:8; PTX 990 at 4d.) Similarly, Dr. Grant demonstrated how a calibration curve based on number average molecular weight value (which is smaller than the peak molecular weight value and therefore corresponds to a time to the right of the peak) of self-standards is adjusted. (Sept. Tr. (Grant) 1408:9-24; PTX 990 at 4f.) The adjustment would, in effect, move the weight average molecular weights to earlier times—to the left (because larger molecules come out of the size exclusion column before smaller molecules). This would have the effect of sliding the light scattering calibration curve to the left. (Sept. Tr. (Grant) 1406:18-1407:6.) Similarly, the adjustment would have the effect of moving the osmometry curve to later times—to the right. (Sept. Tr. (Grant) 1407:7-1408:24.) The adjustments are shown in the graphs below:

Figure 28

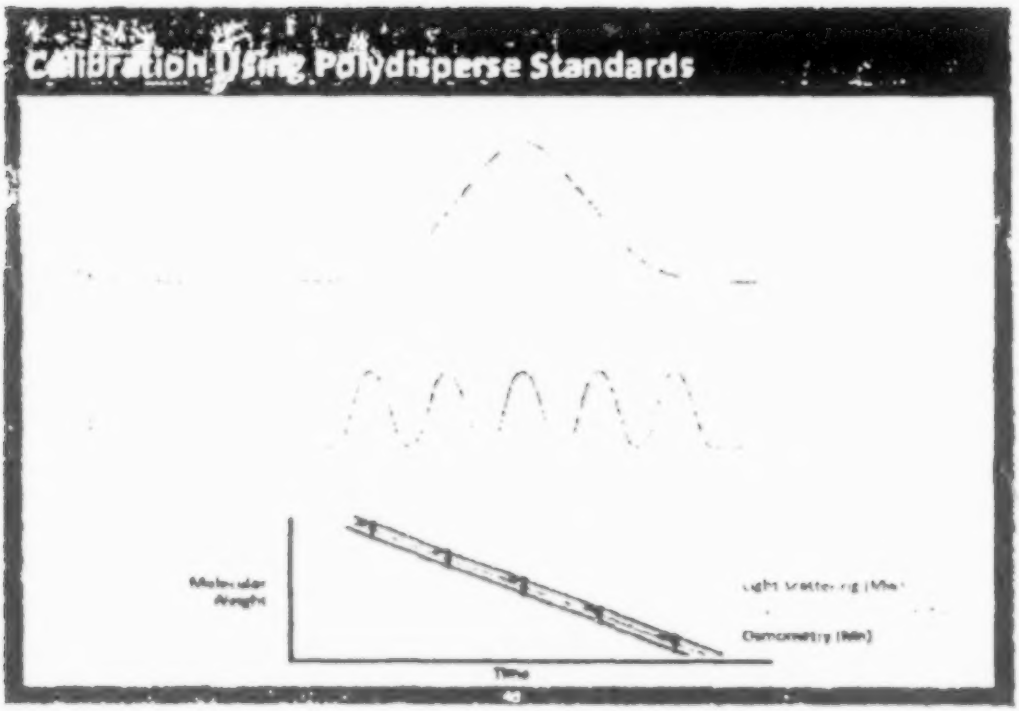
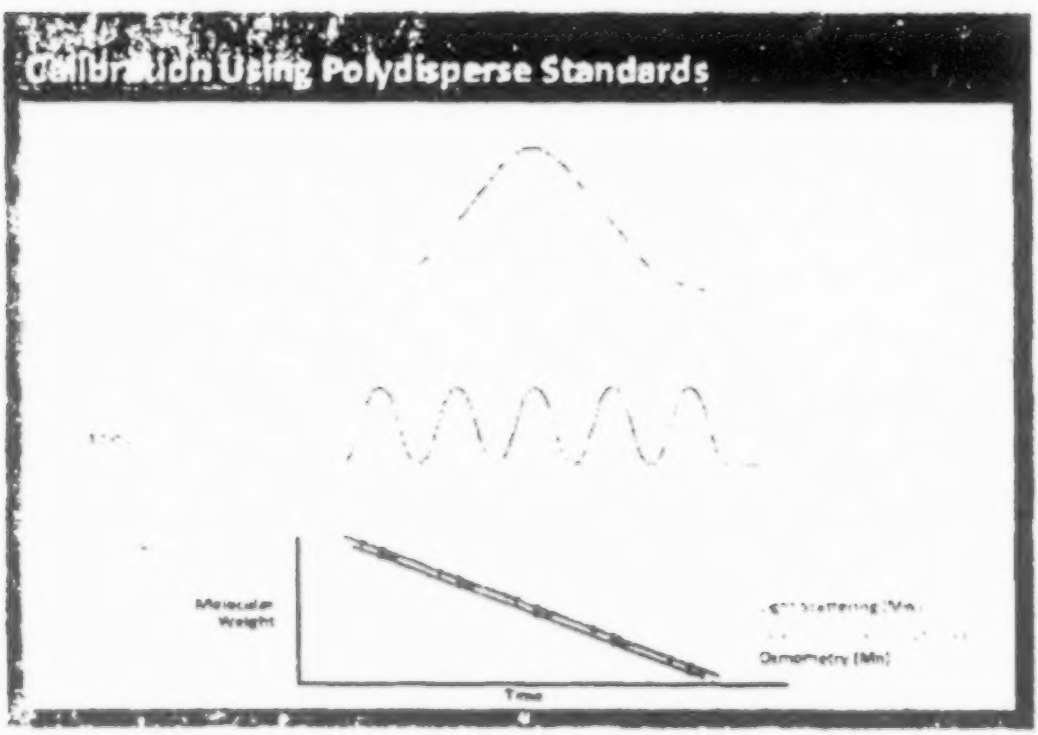


Figure 29



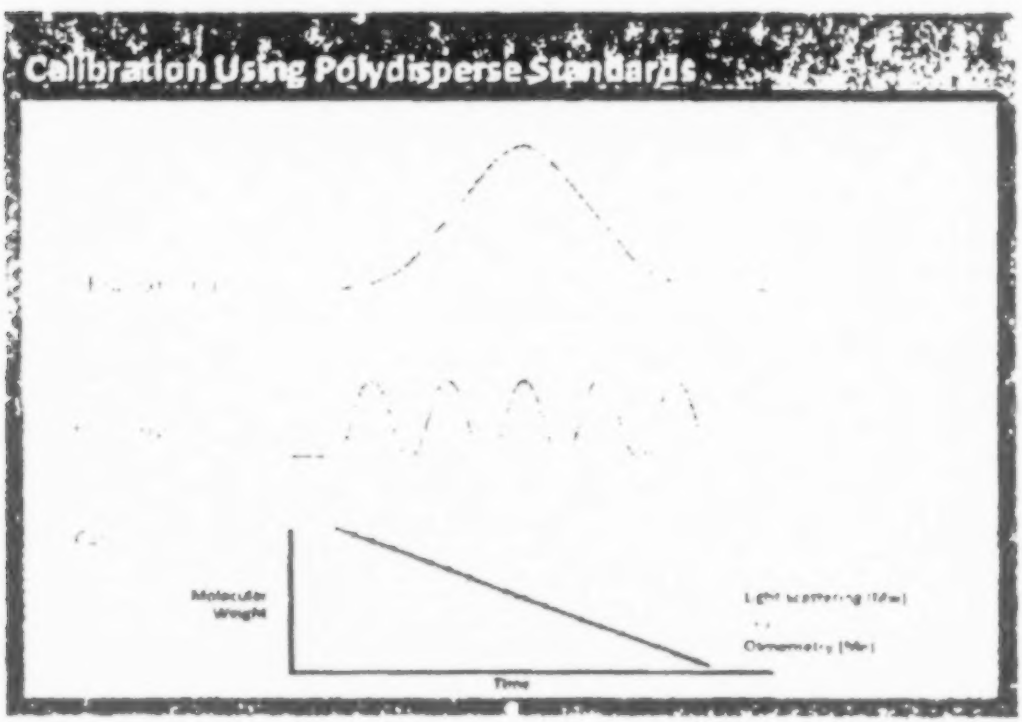
The "end result is that all three calibration curves become one." (Sept. Tr. (Grant) 1408:17-18.)

Dr. Grant further explained how the single calibration curve could be used to obtain an accurate molecular peak molecular weight for a sample:

> At the end of the day, what this means is that you in fact do not have three different calibration curves from which you have to choose which one to use. You in fact have only a single calibration curve that gives you only a single accurate value for the peak of the chromatogram .. .. You locate the time of the peak, come down, find that time on your calibration curve, and you go over and read the molecular weight.

(Sept. Tr. (Grant) 1409:5-16; PTX 990 at 4i.)

Figure 30



Dr. Scandella agreed that techniques for correctly applying the measured average molecular weights of the standards at the correct retention time could have been available in 1994, but testified that he had not "looked at that recently." (Sept. Tr. (Scandella) 1328:7-16.)

iv. Universal Calibration

In 1994, a person of ordinary skill in the art could also have used universal calibration to accurately measure the peak molecular weight and molecular weight distribution (e.g., the percentage of molecules between 2 and 20 kilodaltons or above 40 kilodaltons) of a sample of copolymer-1. (PTX 970 (Svec Dep.) at 320:2-7, 326:14-327:10, 320:22-321:10, 382:8-13, 384:23-385:6, 385:8-19; Sept. Tr. (Grant) 1430:8-1431:23.) According to the theory of universal calibration, the molecular weight values obtained from SEC should not be dependent on the type of standards used for calibration. (PTX 970 (Svec Dep.) at 356:2-8.) Unlike conventional SEC, universal calibration does not require the calibration standards to have the same hydrodynamic volume-to-molecular weight relationship as the sample, because it uses a different physical property—intrinsic viscosity—to allow a correlation of the size of molecules exiting the column to their molecular weight. (Sept. Tr. (Grant) 208:14-20, 1400: 6-15.)

Universal calibration has been known since the late 1960s. By 1994, it was well described in the literature. There was extensive literature on universal calibration and a large number of studies that showed that it worked well for a variety of

different types of polymers. (PTX 970 (Svec Dep.) at 296:16-22; Sept. Tr. (Grant) 1401:15-18, 1423:11-1430:7; PTX 514 at 213-17; PTX 553 at 73-76.) Furthermore, the ability to measure intrinsic viscosity was routine for persons of skill in the art in 1994. (PTX 970 (Svec Dep.) at 296:23-297:6.)

In 1994, a person of ordinary skill in the art could have used the available scientific literature to set up and carry out universal calibration in order to determine the molecular weight of copolymer-1 without significant experimentation. (Sept. Tr. (Grant) 1431:24-1432:11.) Sandoz's universal calibration expert, Dr. Frantisek Svec, agreed that universal calibration could be used to obtain accurate molecular weight results for a sample, and further that universal calibration could be used to obtain accurate molecular weights for copolymer-1:

Q. So in your opinion a person of skill in the art could take a copolymer-1 sample and determine an accurate molecular weight?

A. Yes. Take a sample and determine the molecular weight.

(PTX 970 (Svec 05/21/2010 Dep.) at 388:8-12.)

Based on the foregoing, the Court makes the following conclusions of law in connection with Defendants' arguments.

v. Teva's Experimentation with Copolymyer-1

Defendants make two arguments that are not specific to self-standards or universal calibration. The first is based on Teva's experience with copolymer-1. Sandoz claims that from 1987 to 1998, Teva and its consultants (W.R. Grace) used a number of different standards and analytical methods to attempt to measure the molecular weight of copolymer-1, including at least the following standards: globular proteins, polyethylene glycol, denatured proteins, histones, polylysines, self-standards, and synthetic peptide standards; and at least the following analytical methods: SEC, viscometry, ultracentrifugation, osmometry, MALLS, MALDI-TOF mass spectrometry. (See e.g., DTX 1762; DTX 3275; DTX 1269; DTX 1192; DTX 1701; DTX 1764; DTX 3507; DTX 3540.) According to Sandoz, Teva's experimentation from 1987 to 1998 is probative of the complexities of copolymer-1 and the disparate molecular results one would have obtained without knowledge of the standards and analytical methods Teva used.

Even assuming Teva's scientists and consultants were persons of ordinary skill in the art,[22] the fact that Teva experimented with different standards and analytical methods does not constitute clear and convincing evidence of lack of enablement because

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[22] See Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1374 (Fed. Cir. 1999) ("it defies common sense that [the inventor] would waste valuable resources conducting experiments in other organisms had he not believed that his research associates possessed sufficient skill to perform them").

Defendants never established why Teva experimented with different standards and analytical methods. Without a firm basis for understanding why Teva experimented with different standards and analytical methods, the Court is unable to attach any particular significance to Teva's experimentation or the results described in Teva's and W.R. Grace's memoranda. Indeed, based on the totality of the evidence before the Court, it is entirely plausible that Teva experimented with different methods to deal with regulatory and other scale-up issues, rather than to correct faulty measurements, as Sandoz claims. (See DTX 1770 at TEV000283327.) As a result, the fact that Teva experimented with copolymer-1 from 1987 to 1998 does not, in and of itself, constitute clear and convincing evidence of lack of enablement.

Sandoz's second argument is that, in 1994, it would have been reasonable for a person of ordinary skill in the art to use commercially available protein standards to measure the molecular weight of copolymer-1. Proteins, like copolymer-1, "are polypeptides and . . . there were no other polypeptide molecular weight standards available." (Sept. Tr. (Scandella) 1231:7-13.) In addition, the Superose 12 manufacturer, Pharmacia, recommended globular proteins as the calibration standards for the column. (Sept. Tr. (Scandella) 1231:7-13, 1235:20-1236:17; PTX 752 at TEV000953898.) Using protein standards in 1987, however, Teva found that "[t]he molecular weights of COP-1 batches calculated from the calibration curve of the markers . . were 4-5 times higher than those obtained by viscosity and ultracentrigue." (DTX 3275 at TEV000304994-95,

TEV000304998; Sept. Tr. (Scandella) 1231:16-25.) Because the patents-in-suit failed to disclose this finding, Sandoz argues, if a person of ordinary skill in the art attempted to calibrate the SEC column with commercially available proteins in 1994, that person would not have known that the results were four to five times higher than results obtained from other methods. (Sept. Tr. (Scandella) 1232:20-1233:1.)

The fact is, however, in 1994, a person of ordinary skill in the art would have understood that the polypeptides in copolymer-1 are not globular. (Sept. Tr. (Grant) 1425:12-23; PTX 970 (Svec Dep.) at 395:21-395:24, 396:16-397:8, 397:11-397:17, 397:24-398:15.) As a result, a person of ordinary skill in the art would have understood that globular proteins do not have the same hydrodynamic characteristics as copolymer-1 and thus that they were inappropriate for use in conventional calibration of copolymer-1, as they would provide an inaccurate molecular weight.[23] (Sept. Tr. (Grant) 272:19-273:25, 1399:8-17; PTX 970 (Svec Dep.) at 394:23-395:3, 398:16-398:25; Sept. Tr. (Scandella) 1290:20-23 ("One would start with globular protein standards, test them, find out that they didn't give accurate molecular weights, go

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[23] Dr. Scandella testified that proteins could be appropriate SEC calibration standards if the results were reported "relative to globular protein standards." (Sept. Tr. (Scandella) 1235:7-13.) Because the patents-in-suit did not make such a notation, however, a person of ordinary skill in the art would not have found that such standards were appropriate given that that person would have known that protein standards would give inaccurate results.

on to survey other commercially available standards . . ").)

vi. Self-Standards

Defendants make numerous arguments regarding why self-standards would not have been sufficient to enable the patents-in-suit. None of these arguments, however, constitute clear and convincing evidence of lack of enablement.

As an initial matter, Sandoz does not challenge that a person of ordinary skill in the art could have made copolymer-1 self-standards in 1994 using whole polymer or fractionated self-standards. In fact, Sandoz scarcely challenges any of the literary references Dr. Grant discussed at trial. Instead, it complains that the literature does not teach self-calibration for material as complex or complicated as copolymer-1.[24] Sandoz offers no evidence, however, beyond the conclusory testimony of its experts,[25] which the Court does not credit, that the "complexity" of copolymer-1 presented any particular difficulties with respect to being able to calculate its peak molecular weight or molar fractions using SEC.

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[24] While the literature did not specifically disclose how to measure the molecular weight of copolymer-I, it did describe how to make and use self standards for samples that were, like copolymer-I, polydisperse. (Sept. Tr. (Grant) 1414:22 1418:18, 1419:22-1421:3, 1422:15-1423:10; PTX 514; PTX 553.)

[25] (See Sept. Tr. (Wall) 1812: 17-22 (copolymer-1 "is an incredibly complicated molecule" that "confounds the ability of even very sophisticated investigators to arrive at a molecular weight"); see also Sept. Tr. (Scandella) 1206:9-11 ("The task of creating standards that match a sample as complicated as cop 1 is quite difficult and [may] take years.").)

Defendants next argue that even if self-standards were used for calibration, one would have obtained a wide range of molecular weight results for copolymer-1 self-standards depending on the analytical method chosen. They argue further that it is not only the type of molecular weight average (Mz vs. Mw vs. Mn) that would vary depending on the method, but also that the molecular weight values themselves would vary across methods, even for the same type of average. While Defendants cite to several seemingly problematic tables and/or batches, Defendants fail to establish that these results were anything more than outliers, which Teva and its consultants knew were wrong.

Sandoz points first to a November 1995 table in a Teva document that lists 15 copolymer-1 markers and their average molecular weights obtained by ultracentrifugation, viscometry, and MALLS. (DTX 3509 at TEV001116167.) The table shows that depending on the method that was used, the molecular weight for a given standard varied by up to 2,100 daltons (marker 02095 [5,800-7,900 daltons]) in the lower end of the molecular weight range and up to 3,000 daltons in the upper end of the range (marker BD-402 [22,200-25,200 daltons]). (DTX 3509 at TEV001116167.)

In an effort to buttress the variability shown in Teva's November 1995 table, Sandoz cites an August 1995 document that appears to list the Mw and Mn MALLS results for the same 15 markers (DTX 1699 at TEV000950015), and another document that appears to list additional Mw and Mn results from other molecular weight analyses on the same

markers (DTX 1642 at TEV001013041, TEV001013087). Comparing results from separate tables across documents, Sandoz claims, without any expert support or other testimony regarding the validity of the results, that there was a variation of nearly 5,000 daltons for the Mn values (5,200-10,100 daltons) (compare DTX 1699 at TEV000950015 with DTX 1642 at TEV001013041) and a variation of 9,000 daltons for the Mw values (5,800-14,800 daltons) (compare DTX 1699 at TEV000950015 with DTX 1642 at TEV001013041) depending on the analytical method that was used. Sandoz goes on to claim, again without any expert support or other testimony regarding the validity of the results, that the Mw value of marker BD-402 varied from 22,200 to 48,900 daltons depending on the selected method. (Compare DTX 1699 at TEV000950015 with DTX 1642 at TEV001013041.)

Without any expert testimony that the results in the Tables in DTX 1699 and 1642 can be compared in any meaningful way—much less with the results in Teva's November 1995 table—the Court cannot find that the tables in DTX 1699 or DTX 1642 constitute clear and convincing evidence of variability across different analytical methods. The Court notes that it precluded Sandoz's expert, Dr. Wall, from testifying about DTX 1699 and DTX 1642 on the last day of trial because he had failed to provide any notice prior to that time, pursuant to Rule 26 of the Federal Rules of Civil Procedure, that he intended to offer opinions regarding the results in these documents and it came as a surprise to Teva. (Sept. Tr. 1793:5-11.) The Court expressly admonished defense counsel not to make legal arguments about these (or any

other technical) documents without expert testimony. (Sept. Tr. 1795:9-19.)

Sandoz's next argument in support of variability involves a single batch of copolymer-1. Depending on the analytical method that was used, according to Sandoz, batch 13 yielded different molecular weights for the same sample. (See DTX 3581 at 12; see also Sept. Tr. (Scandella) 1259:13-1260:15.)

The first document Sandoz cites is a May 4, 1988 report from W.R. Grace, which reports the molecular weights of copolymer-1 obtained using an SEC column calibrated with protein standards. (DTX 1762 at TEV003017835.) At trial, Dr. Grant testified that the report itself suggests that the authors "knew full well" that protein standards were not appropriate for copolymer-1. (Sept. Tr. (Grant) 324:15-325:5; DTX 1762 at TEV003017833.) Indeed, the report explicitly states, "Calibration curves based on globular proteins yield COP-1 molecular weights 4-6 times higher than molecular weights calculated by ultracentrifugation or viscosity measurements." (DTX 1762 at TEV003017833.) Moreover, by May 4, 1988, the date of this report, Teva was already using copolymer-1 self-standards and had developed a molecular weight method based on those standards. (Sept. Tr. (Grant) 322:4-13, 1450:13-18, 1451:23-1452:3, 1462:18-23, 1569:7-11; Sept. Tr. (Scandella) 1307:22-1308:2; Sept. Tr. (Wall) 1828:21-1829:5; DTX 3275 at TEV000304999-5000.)

The second document Sandoz relies on is a September 9, 1988 report from W.R. Grace, which discusses the use of polyethylene glycol ("PEG")

standards. (DTX 1269.) Sandoz contends that this document demonstrates that different standards yield different results for a copolymer-1 sample. At trial, however, Dr. Grant testified that W.R. Grace's task, as explained in the report, was to look at other analytical techniques and use them for the purpose of determining whether or not a batch of copolymer-1 was active or toxic. (Sept. Tr. (Grant) 1455:24-1456:11.) While the report discusses PEG standards, it states that they were used for a relative molecular weight estimation ("vs. polyethylene glycol standards"). (DTX 1269 at TEV001090148.) Dr. Grant testified that one skilled in the art would not have believed that using PEG standards (without universal calibration) would give an accurate molecular weight for copolymer-1 because the person of skill would have known that the size-to-molecular-weight ratio of PEG is not the same as copolymer-1. (Sept. Tr. (Grant) 1457 :20-24.)[26] The Court credits Dr. Grant's testimony.

Sandoz characterizes the W.R. Grace report as showing molecular weights of fractions of copolymer-1 batch 13 as ranging from 800 to 11,000 daltons using the PEG standards. But, as Dr. Scandella acknowledged, these values are for the copolymer-1 fractions, not the average molecular weight of the batch. (Sept. Tr. (Scandella) 1248:22-25.) Dr. Grant testified that the data have nothing to do with the

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[26] On the other hand, Dr. Grant testified, PEG standards, which were commercially available in 1994, could have been used as universal calibration standards for copolymer-I. (Sept. Tr. (Grant) 1426:4 15, 1504:2 4; Sept. Tr. (Scandella) 1248:12 18.)

peak molecular weight of a batch of copolymer-1. (Sept. Tr. (Grant) 1458:1-14.)

Sandoz also relies on the September 9, 1988 W.R. Grace report for its conclusion that vapor phase osmometry would yield erroneous molecular weight values for copolymer-1. The portion of the document Sandoz cites, however, has nothing to do with SEC; it relates to an entirely different technology. As Dr. Grant testified, determining Mn using osmometry is completely different from determining Mp using SEC. (Sept. Tr. (Grant) 1570:8-12.) In addition, Dr. Grant pointed out that there are different types of osmometry, some of which would be appropriate in the context of this case and others that would not. Dr. Grant testified that vapor phase osmometry would not have been an appropriate method to measure the molecular weight of a copolymer-1 standard (Sept. Tr. (Grant) 1506:21-1507:9), but that membrane osmometry would have been more appropriate for copolymer-1 (Sept. Tr. (Grant) 1569:21-1570:7). Dr. Scandella, who testified that vapor phase osmometry was considered an appropriate method, failed to mention the existence of different kinds of osmometry, and conceded that he had not looked at the literature on the appropriateness of vapor phase osmometry. (Sept. Tr. (Scandella) 1318:14-1319:1.) Significantly, W.R. Grace itself acknowledged in the report that it did not believe vapor phase osmometry gave an accurate molecular weight of copolymer-1. (Sept. Tr. (Grant) 1459:5-11, 1460:8-13; DTX 1269 at TEV0 010 90158.)

Because the scientists in the documents Sandoz relies on regarding batch 13 understood that the

values they were reporting were erroneous, Sandoz's argument regarding batch 13 fails.

Lastly, for all of Defendants' arguments regarding the different techniques that Teva used and the allegedly inconsistent results that Teva obtained, Defendants did not cite a single instance where Teva—or anyone for that matter—failed to accurately calculate the peak molecular weight or the molar fraction of copolymer-1.

vii. Universal Calibration

Defendants make several arguments regarding why universal calibration would not have enabled the patents-in-suit. Their first argument is that universal calibration was not identified in the patents-in-suit. This argument fails because a patent need not provide details that would be known and available to those of skill in the art. Singh v. Brake, 317 F.3d 1334, 1345 (Fed. Cir. 2003) ; see also Ajinomoto Co., 228 F.3d at 1345; United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986). By 1994, universal calibration was well described in the literature and known to a person of ordinary skill in the art. (PTX 970 (Svec Dep.) at 296:16-297:6; Sept. Tr. (Grant) 1401:15-18, 1423:11-1430:7; 1431:24-1432:11; PTX 514 at 213-17; PTX 553 at 73-76.) At his deposition, Dr. Svec, Sandoz's expert with experience in universal calibration, testified that universal calibration could be used to accurately determine the molecular weight of copolymer-1. (PTX 970 (Svec 05/21/2010 Dep.) at 388:8-12, 320:2-321:10, 326:14-

327:10, 382:8-13, 384:23-385:6, 385:8-19.) Thus, there was no reason the patents needed to identify or mention universal calibration.

Defendants' second argument is that there is no evidence that Teva or its consultants ever used universal calibration despite the fact that they were aware of it. In support of this argument, Sandoz cites a May 23, 1988 memo from W.R. Grace.

(DTX 3538 at TEV000360384.) The very fact, however, that Teva and its contractors were aware of universal calibration in 1988 merely proves that universal calibration was known and available long before 1994. In addition, Defendants offered no evidence regarding why Teva, although apparently aware of universal calibration, did not use it to measure the molecular weight of copolymer-1. Without any evidence on this issue, the Court is unable to draw any conclusions regarding why Teva did not use universal calibration.

Relying on Dr. Scandella's testimony, Defendants' third argument is that universal calibration was not a common technique in biotechnology in 1994 and 1995. (See Sept. Tr. (Scandella) 1284:13-18.) But neither Defendants nor Dr. Scandella ever demonstrated a connection between copolymer-1 and biotechnology, or any other relevance of Dr. Scandella's testimony on this point with respect to the issues in this case. In addition, neither Defendants nor Dr. Scandella address the literature Dr. Grant described, which explained universal calibration and made it clear that universal calibration was a well-known technique in 1994.

(Sept. Tr. (Grant) 1401:12-18; 1423:11-1430:7; PTX 514 at 213-17; PTX 553 at 73-76.) Moreover, neither Defendants nor Dr. Scandella addressed the fact that by 1994 universal calibration had been known and used for nearly three decades. For these reasons, Dr. Scandella's opinion does not support the position that universal calibration was not a well-known technique in 1994 for determining the molecular weight of copolymer-1.[27]

Defendants' final argument, based entirely on attorney argument, is that characteristics of copolymer-1 would impede a person of ordinary skill in the art from using universal calibration to accurately determine the molecular weight of copolymer-1. Quoting Dr. Scandella, who referenced "ion exchange interactions," Sandoz argues that factors other than size can influence retention time. (Sept. Tr. (Scandella) 1200:1-4.) But Dr. Scandella's testimony had no connection to universal calibration. Defendants presented no evidence at trial that any interactions occur between copolymer-1 and the column matrix or that there would have been any concerns about any such interactions on the part of a person of ordinary skill in the art in 1994. Defendants also failed to provide any evidence that "ion exchange interactions" were relevant to universal calibration.

Without any supporting explanation from an expert, Defendants quote one sentence from a 1989

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[27] As of 1994, Dr. Scandella had never used universal calibration. When asked why, he replied, "I never found a need for it. (((Sept. Tr. (Scandella) 1285:14)

article by Marc le Maire that states, "[o]ur data indicate that the concept of universal calibration requires several qualifications and can be used only as an approximation in most cases." (See DTX3353 at 51.) Dr. Scandella read this sentence into the record, but offered no expert opinion that it is relevant, in any way, to this case. (See Sept. Tr. (Scandella) 1287:14-1288:1.) In fact, neither Dr. Scandella nor any other expert in this case testified that universal calibration was not known and readily available, that it would not have worked, or that it would have taken undue experimentation to use the technique on copolymer-1 in 1994.

Pointing to Grant's testimony on direct examination, Sandoz also suggests that universal calibration applies only to flexibly coiled molecules (i.e., random coils). (Sept. Tr. (Grant) 1425:7-23).) However, neither Dr. Grant nor the textbook about which he was questioned, states that universal calibration is limited to random coils. (See Sept. Tr. (Grant) 1425:1-6; see also PTX 514 at 213.) Defendants also introduced no evidence to this effect at trial. More importantly, both Dr. Grant and Defendants' expert, Dr. Svec, agreed that polypeptides in copolymer-1 are random coils, and both of them explained in detail why a person of ordinary skill in the art would have understood that to be the case in 1994. (See Sept. Tr. (Grant) 1425:12-23, 1427:1-9; see also PTX 970 (Svec 05/21/2010 Dep.) at 395:21-24, 396:16-397:8, 397:11-17, 397:24-398:15.)

Defendants contend that a Teva document indicates that copolymer-1 has a secondary structure

and is not a random coil. (See DTX 1113 at TEV00312034.) Although that is what the document appears to state, the Court credits Dr. Grant's testimony that the document does not contain enough information for him to evaluate it. (Sept. Tr. (Grant) 1535:18-1536:11.) The Court also gives more weight to Dr. Grant's and Dr. Svec's opinion that polypeptides in copolymer-1 are random coils. (See Sept. Tr. (Grant) 1425:12-23, 1427:1-9; see also PTX 970 (Svec 05/21/2010 Dep.) at 395:21-24, 396:16-397:8, 397:11-17, 397:24-398: 15.)

Defendants also point to another sentence in the le Maire article, which they did not even bother to have an expert read into the record at trial, to argue that even if the structure of copolymer-1 were a random coil, the use of universal calibration would still be problematic. The sentence reads that the "ambiguity in defining the molecular radius of macromolecules such as random coils and long rods ... represents an obstacle to universal calibration of gel columns." (DTX 3353 at 55.) The sentence does not say that universal calibration would not work with copolymer-1 or that using universal calibration would require undue experimentation. And, as explained above, Defendants provided no expert testimony to this effect at trial. Defendants essentially make this argument on attorney argument alone. As Teva points out, in another section of the le Maire paper, the authors indicate that universal calibration will work with random coils. The section states that "rather good agreement between the viscosity and gel chromatography data was obtained for dextran and proteins denatured with GuHCl [guanidine hydrochloride] .. For

proteins denatured in 6 M GuHCl the peptide chain has been described as a random coil." (DTX 3353 at 55.) Without any expert testimony to resolve these seemingly inconsistent statements in the le Maire article, the Court cannot accept Defendants' argument.

viii. In re Wands Factors

Turning to In re Wands, with respect to the first factor— "the quantity of experimentation necessary"—the Court finds that Defendants failed to provide clear and convincing evidence that the amount "of experimentation necessary" to accurately determine the average molecular weight or molecular weight distribution of a sample of copolymer-1, in 1994, was undue. The patents-in-suit specifically direct a person of ordinary skill in the art to use SEC. (PTX 1 at 3:6-8.) Although the patents-in-suit did not disclose the SEC calibration standards that Teva used, the evidence at trial established that, in 1994, the scientific literature on SEC, generally, and on both self-standards and universal calibration was extensive and would have been known to a person of ordinary skill in the art.[28] (See PTX 514 at 210-17; see also Sept. Tr. (Grant) 1400:16-19, 1401:9-11, 1401:15-18, 1408:25-1409:4, 1410:10-1413:23, 1414:8-1421:18, 1423:11-1430:7; PTX 566 at 37-44; PTX 970 (Svec Dep.) at 296:16-

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[28] The extensive body of scientific literature, in 1994, regarding SEC generally and on both self-standards and universal calibration establishes that "the state of the prior art"-the fifth In re Wands factor-was well developed. See In re Wands, 858 F.2d at 737 (citation omitted). The "state of the prior art," accordingly, supports a finding of enablement.

297:6; PTX 553 at 73-76.) Because "v [a] patent need not teach ... what is well known in the art,'" the fact that the patents-in-suit did not disclose the SEC calibration standards that Teva used does not constitute clear and convincing evidence that accurately determining the average molecular weight or molecular weight distribution of a sample of copolymer-1 in 1994 would have required undue experimentation. See, e.g., Falko-Gunter Falkner, 448 F.3d at 1365 (citation omitted).

The Court rejects Dr. Scandella's testimony that experimentation may have taken "several years." (Sept. Tr. (Scandella) 122 7:21-122 8:11; 1291:18-25.) As an initial matter, Dr. Scandella failed to address the extensive literature that existed in 1994 regarding SEC, self-standards, and universal calibration. (See PTX 514 at 210-17; see also Sept. Tr. (Grant) 1400:16-19, 1401:9-11, 1401:15-18, 14 08:25-1409:4, 1410:10-1413:23, 1414:8-1421:18, 1423:11-143 0:7; PTX 566 at 37-44; PTX 970 (Svec Dep.) at 296:16-297:6; PTX 553 at 73-76.) In addition, Dr. Scandella assumed, but never established, that Teva experimented with different standards and analytical methods because it could not accurately determine the molecular weight of copolymer-1. As explained above, Defendants never established why Teva experimented with different standards and analytical methods.

To the extent some experimentation was necessary to accurately determine the average molecular weight or molecular weight distribution of a sample of copolymer-1 in 1994, a fact Teva does not deny and the precise amount of which was not established at

trial,[29] the law is well-settled that where the level of skill in the art is high, as was the case here,[30] (Sept. Tr. (Grant) 189:22-190:6; PTX 986 at 3); Sept. Tr. (Scandella) 1190:15-20, 1300:20-1301:9; Sept. Tr. (Zeiger) 809:10-811:15; DTX 4030 at 4), "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered 'undue.'" See Falko-Gunter Falkner, 448 F.3d at 1365 (internal quotation marks omitted); see also Chiron Corp., 363 F.3d at 1253 ("[t]he fact that some experimentation is necessary does not preclude enablement") (citations and internal quotation marks omitted). In view of the patents-in-suit reference to "a calibrated gel filtration column (Superose 12)," (PTX 1 at 3:7-8), and the extensive literature in 1994 regarding SEC, self-standards, and universal calibration, "'a considerable amount of experimentation is permissible'" here. See PPG Indus., Inc., 75 F.3d at 1564 (citation omitted).

ix. The Patents-in-Suit Provided Sufficient Direction or Guidance

The patents-in-suit specifically direct a person of ordinary skill in the art to use SEC. (PTX 1 at 3:6-8.) In addition to this explicit directive, the evidence at trial established that, in 1994, there was extensive

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[29] At his deposition, Varkony testified that he could not "say exactly if it" took "several weeks or more" for Teva to figure out how to calibrate SEC to determine the molecular weight of copolymer-I. (DTX 4022 at 110:10-18.)

[30] "[T]he relative skill of those in the art" is the sixth In re Wands factor. 858 F.2d at 737 (citation omitted).

scientific literature on SEC, self-standards, and universal calibration, which would have been known to a person of ordinary skill in the art. (See PTX 514 at 210-17; see also Sept. Tr. (Grant) 1400:16-18, 1401:9-11, 1401:15-18, 1414:8-1418:6, 1419:13-1421:3, 1421:4-18, 1423:11-1430:7; PTX 566 at 37-44; PTX 970 (Svec Dep.) at 296:16-297:6; PTX 553 at 73-76.) In view of this extensive body of scientific literature, the Court finds that the patent specification's instruction to use SEC would have been sufficient guidance for a person of ordinary skill in the art to accurately determine the average molecular weight and molecular weight distribution of a sample of copolymer-1 in 1994.

Example 1 of the patent explicitly discloses the use of SEC to determine the average molecular weight of copolymer-1 samples. (PTX 1 at 2:51-3:18.) The example discloses that the molecular distribution of the copolymer-1 samples was determined using a calibrated size exclusion chromatography column. (PTX 1 at 3:9-18.) The fact that the patents-in-suit include a working example supports a finding of enablement. See, e.g., In re Wands, 858 F.2d at 740 (finding no undue experimentation, where disclosure presents working examples).

Defendants argue that copolymer-1 is complex. This argument fails, however, because, in 1994, high molecular weight copolymer-1 was known in the prior art. In addition, the concept of molecular weight and the measurement of molecular weight

using SEC were well known in 1994.[31] There was also a significant quantity of scientific literature describing SEC and its use for determining the molecular weight of polydisperse polymers such as copolymer-1. Under these circumstances, there is nothing about the nature of the claimed invention that supports a finding that the claims are not enabled.

Defendants argue that the "chemical arts" are unpredictable, and that no prior art provides any guidance on making the claimed invention because the claimed molecular weight ranges are relative to the SEC standards chosen by the patentees. A significant body of scientific literature, however, described molecular weight determination using SEC in 1994. In addition, Defendants presented no evidence of unpredictability relating to measuring the peak molecular weight of copolymer-1. Quoting a case that states that the "chemical arts" are unpredictable does not establish that the use of SEC with respect to copolymer-1 was unpredictable. As described above, there is no evidence that a person of skill in the art would have needed to know the specific SEC standards used by the patentees in order to make and use copolymer-1 within the scope of the claims without undue experimentation. See Koito Mfg. Co. Ltd. v. Turn-Key-Tech, LLC, 381 F.3d

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[31] The fact that high molecular weight copolymer-1 was known in the prior art, coupled with the fact that there was an extensive body of scientific literature, in 1994, regarding SEC generally and on both self-standards and universal calibration, demonstrates that "the state of the prior art" was well developed. See In re Wands, 858 F.2d at 737 (citation omitted).

1142, 1156 (Fed. Cir. 2004); see also Telectronics, 857 F.2d at 785; Hybritech, 802 F.2d at 1384.

To the extent Defendants argue that the specification must enable one of ordinary skill in the art to make Copaxone®, the Court rejects this argument. Copaxone® is a pharmaceutical product with an average molecular weight between 5,000 and 9,000 daltons. The patents-in-suit enable a person of ordinary skill in the art to make copolymer-1 with an average molecular weight within that range. Copaxone®, however, the commercial product, has many additional characteristics besides molecular weight. Contrary to Defendants' argument, there is simply no requirement that the patents enable a person of ordinary skill in the art to match all of the characteristics of Copaxone®.[32]

D. INDEFINITENESS

i. General Principles

Since patents are "presumed to be valid, the evidentiary burden to" prove indefiniteness "is one of clear and convincing evidence." See Young v. Lumenis, Inc., 492 F.3d 1336, 1345 (Fed. Cir. 2007) (citation omitted). To satisfy Section 112's "definiteness requirement, the boundaries of the claim, as construed by the court, must be discernible

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[32] To the extent the Court has not explicitly addressed the seventh and eighth In re Wands factors above, the Court finds that Defendants failed to present any persuasive evidence that "the predictability or unpredictability of the art" or "the breadth of the claims" supports a finding of lack of enablement. 858 F.2d at 737 (citation omitted).

to a skilled artisan based on the language of the claim, the specification, and the prosecution history, as well as her knowledge of the relevant field of art." Power-One, Inc. v. Artesyn Techs., Inc., 599 F.3d 1343, 1350 (Fed. Cir. 2010) (citation omitted). A claim is indefinite when it "is 'not amenable to construction or [is] insolubly ambiguous.'" Id. (citation omitted). "[A] claim is not indefinite merely because it poses a difficult issue of claim construction." Id. (citation omitted). "'[I]f the meaning of the claim is discernible, even though the task may be formidable and the conclusions may be one over which reasonable persons will disagree, .. the claim [is] sufficiently clear to avoid invalidity on indefiniteness grounds.'" Id. (citation omitted). In addition, "the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite." Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1379 (Fed. Cir. 2001) (citation omitted).

ii. None of the Asserted Claims Are Indefinite

Defendants argue that the Court's construction of the molecular weight terms as being measured using an "appropriately calibrated suitable gel filtration column" results in an insoluble ambiguity because there were different ways to "appropriately" calibrate an SEC column, and because the different calibrations would not yield the same molecular weight values. Accordingly, Defendants argue, all of the claims that contain the limitation "coopolymer-1 having a molecular weight" or "average molecular

weight" or that are a "molar fraction" or "species" claims are indefinite.

The Court finds, as an initial matter, that "appropriate" standards are those that yield "accurate" molecular weight measurements. (See Sept. Tr. (Grant) 1505:17-22.) A measurement is "accurate" if it reflects the actual molecular weight of the sample. (See Sept. Tr. (Grant) 218:12-14; see also PTX 970 (Svec 5/21/2010 Dep.) at 321:5-10.) As the Court found and explained above, in 1994, there were at least two ways to accurately measure the molecular weight of copolymer-1 using SEC—namely, self-standards and universal calibration. (See Sept. Tr. (Grant) 1399:18-1400:13; PTX 990 at 2.) SEC is the only method mentioned in the patents-in-suit, and the only method that can generate a peak molecular weight and a molecular weight distribution (Sept. Tr. (Scandella) 1205:20-1206:1)-and all of the experts agreed that SEC can give an accurate molecular weight for copolymer-1. (See Sept. Tr. (Grant) 217:23-218:14, 1399:18-1400:13, 1421:19-1422:8, 1430:8-1431:23, 1462:18-23; PTX 970 (Svec 5/21/2010 Dep.) at 320:2-321:10; Sept. Tr. (Scandella) 1312:2-14; PTX 209 at SDZ00002017-18; PTX 349 at SDZ00017948-49.)

Defendants failed to present clear and convincing evidence that a person of ordinary skill in the art using SEC with appropriate calibration could not achieve consistent and reproducible molecular weight values. To the extent Defendants point to outlier measurements of copolymer-1 in Teva's internal documents, as the Court found and explained above, those batches were recognized as

erroneous in the contemporaneous documents. In addition, with respect to batches that used protein standards, those standards were inappropriate because they do not provide accurate molecular weights.

In the final analysis, the evidence presented at trial shows that a person of skill in the art in 1994 would have known how to appropriately calibrate an SEC column to obtain accurate molecular weight values for copolymer-1. Accordingly, the Court finds that none of the asserted claims are indefinite.

E. OBVIOUSNESS

Defendants argue that the patents-in-suit would have been obvious to a person of ordinary skill in the art as of May 24, 1994, the filing date of the '037 application. Defendants claim that copolymer-1 falling within the claimed average molecular weight range, or having the claimed molecular weight distribution, would have been obvious based on the teaching in the prior art. They also argue that certain process limitations to make copolymer-1 within the desired molecular weight—such as the use of HBr in acetic acid—were obvious.

i. General Principles

Obviousness is a question of law based on underlying factual questions. Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1300 (Fed. Cir. 2007). "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that

the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103.

To determine whether a claim is obvious, the Court must consider "(1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) evidence of secondary factors, also known as objective indicia of non-obviousness." Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd., 533 F.3d 1353, 1356 (Fed. Cir. 2008). The first three factors "comprise the so-called prima facie case" of obviousness. Mitsubishi Chem. Corp. v. Barr Labs., Inc., 718 F Supp. 2d 382, 425 (S.D.N.Y. 2010), aff'd, 435 Fed. Appx. 927 (Fed. Cir. 2011).

With respect to the contents of the prior art, the question is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." In re Gorman, 933 F.2d 982, 986 (Fed. Cir. 1991). The well-established rule is that an invention is obvious in light of the prior art if "a person of ordinary skill in the art would have had motivation to combine the prior art references and would have had a reasonable expectation of success in doing so." Wyers v. Master Lock Co., 616 F.3d 1231, 1238 (Fed. Cir. 2010) (en banc) (citations omitted). Where the invention has elements that were described in the prior art, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." Takeda Chem. Indus., Ltd. v.

Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007).

Where prior art would lead a person of skill away from the invention, the art is said to "teach away" from the invention. DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1327 (Fed. Cir. 2009). The patent holder can rebut a prima facie case of obviousness by showing that the prior art taught away from the invention. Whether the prior art taught away from the invention is a question of fact. Spectralytics, Inc. v. Cordis Corp., 649 F.3d 1336, 1343 (Fed. Cir. 2011).

A patent holder can also rebut a prima facie case of obviousness with evidence of secondary considerations of non-obviousness. Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc., 617 F.3d 1296, 1304-05 (Fed. Cir. 2010). Such evidence includes the extent of commercial success of the patented invention, unexpected properties of the invention, whether the invention satisfies a long-felt need, whether others have failed to find a solution to a problem addressed by the patent, and any copying of the invention by others. See Transocean Offshore Deepwater Drilling, Inc., 617 F.3d at 1304-05; Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1380 (Fed. Cir. 2006).

The party asserting invalidity on the ground of obviousness must prove by clear and convincing evidence that "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35

U.S.C. § 103; Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007). In evaluating whether the patent challenger has carried its burden, courts are wary of arguments based on improper hindsight. See In re NTP, Inc., 654 F.3d 1279, 1298-99 (Fed. Cir. 2011).

ii. The Scope and Content of the Prior Art

In this context, "prior art" includes art that is analogous to the claimed invention. In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004). The Court finds the following facts in connection with the scope and content of the prior art.

1) The '550 Patent

The patents-in-suit refer to the '550 patent as a source of the procedure for making copolymer-1. (PTX-1 at 2:15-17) ("[c]opolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550"); Id. at 2:54-56 ("[t]wo batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550").)

The '550 patent, which issued to Yeda on November 19, 1974, describes compositions of several copolymers, including copolymer-1. The '550 patent states that the disclosed copolymers generally have a molecular weight "in excess of 10,000, and preferably above about 18,000" daltons. (Sept. Tr. (Grant)

1435:4-1437:19; Sept. Tr. (Zeiger) 839:18-840:18; PTX 26, col. 1:57-68.)

The only specific disclosure of copolymer-1 in the specification of the '550 patent appears in column 2, lines 19-30 of the patent specification. (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 933:14-934:18; PTX 26, col. 2:19-30.) There, the '550 patent describes a preferred copolymer, which is copolymer-1, having "a molecular weight of about 20,000 to 25,000" daltons. (Sept. Tr. (Grant) 1436:17-1437:9; Sept. Tr. (Zeiger) 933:21-934:4; PTX 26, col. 2:19-30.)

The '550 patent does not state how the average molecular weights reported in the patent were determined or the methodology used to generate the measurement. (Sept. Tr. (Grant) 1434:13-16, 1438:2-7; Sept. Tr. (Zeiger) 939:6-19, 956:10-957:13, 958:23-959:3.) The '550 patent contains no disclosure, teaching, or data regarding the molecular weight distribution or molar fractions of any copolymer. (Sept. Tr. (Grant) 1434:13-16, 1438:16-19; 1439:7-24, 1441:1-25; Sept. Tr. (Zeiger) 956:10-18, 957:2-6; PTX 26; PTX 320 at MYL0000616.)

The examiners of each of the patents-in-suit considered the '550 patent extensively during prosecution of the patents-in-suit. (See, e.g., PTX 14 at TEV000309018; PTX 15 at TEV000309103; PTX 17 at TEV000304221; PTX 18 at TEV000310385; PTX 19 at TEV000304453; PTX 20 at TEV000304582; PTX 21 at TEV000308838.) Ultimately, there were no obviousness rejections

based on the '550 patent. (PTX 13 at TEV000304151-152; PTX 13-21.)[33]

2) EP '62 0 Patent Application

European Patent Application No. 0383620 ("the EP '620 Application"), filed by Repligen Corporation on February 16, 1990 and published on August 22, 1990, discloses a biological process for making genes encoding polypeptides involving the use of recombinant DNA technology. (Sept. Tr. (Grant) 1445:4-22, 1446:23-1447:14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 11, 11. 32-34.) The process described in the EP '620 Application does not involve the chemical synthesis of N-carboxyanhydrides. (Sept. Tr. (Grant) 1445:4-22, 1446:23-1447:14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 2, 11. 50-55.)

The EP '620 Application contains no disclosure or teaching regarding a molecular weight distribution or molar fractions of copolymer-1. (Sept. Tr. (Grant) at 1448:17-19; see generally DTX 1970.) The EP '620 Application does not disclose any copolymers having an "average molecular weight" of 5,000 daltons.

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[33] During the prosecution of the '808 patent, the examiner rejected then pending claims 17-20 as prima facie obvious in view of the '550 patent. (See PTX 13 at TEV000304138-144.) The applicants were able to overcome the obviousness rejection over the '550 patent by arguing that the '550 patent did not raise a prima facie case of obviousness by pointing out to the examiner that the '550 patent did not teach or suggest the claimed invention. (PTX 13 at TEV000304151-152.) The applicants did not rely on secondary considerations or unexpected results to overcome the obviousness rejection based on the '550 patent. (See PTX 13 at TEV000304151-152, 162-167.)

(Sept. Trial (Grant) 1447:15-1448:10; Sept. Trial (Zeiger) 977:17-20.) Further, the EP '620 Application does not disclose measuring the average molecular weight of any copolymer using size exclusion chromatography, i.e., using an appropriately calibrated suitable gel filtration column. (Sept. Trial (Grant) 1448:11-13; Sept. Trial (Zeiger) 976:15-23.)

3) The Teitelbaum 1971 Article and 1974 Abstract

As described above, Professor Ruth Arnon and her colleagues at the Weizmann Institute discovered copolymer-1 in the 1960s, and first published their research on copolymer-1 in the 1971 Teitelbaum article. Because copolymer-1 was modeled after myelin basic protein, Professor Arnon and her colleagues aimed for an average molecular weight of about 23,000 daltons. July Tr. (Arnon) 309:21-311:8. The 1971 Teitelbaum article described copolymer-1 as having an average molecular weight of 23,000 daltons. (July Tr. (Arnon) 311:24-312:22; PTX 499 at 242.)

In September 1974, Professor Arnon and her colleagues at the Weizmann Institute published an abstract reporting that copolymer-1 had been found to suppress EAE, a biological model for multiple sclerosis. (PTX 509 at 1172.) The abstract stated that copolymer-1 has a molecular weight of 23,000 daltons. (PTX 509 at 1172.) The abstract further reported that copolymer-1 compositions with molecular weights lower than 17,000 daltons or higher than 50,000 daltons "proved ineffective for the treatment of EAE." (July Tr. (Arnon) 312:23-313:18;

Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.)

At trial, Dr. Arnon explained that this statement would have deterred a person of ordinary skill in the art from lowering the molecular weight of copolymer-1, (July Tr. (Arnon) 312:23-313:18, 316:25-317:11, 333:7-22), and Dr. Grant concurred with this reading from the perspective of a person of ordinary skill in the art. (Sept. Tr. (Grant) 1442:8-1444:9.) The Court credits that testimony.

4) Prior Art Regarding the Use of HBr/acetic Acid To Achieve Desired Molecular Weight

As discussed, the patentees discovered and described in the patents-in-suit that the process of using HBr in acetic acid during the debenzylation stage would cleave the polypeptides during polymerization and could therefore be used to control the molecular weight of the resulting copolymer-1. (Sept. Tr. (Sampson) 1641:8-23.) The patentees also discovered that a copolymer-1 composition with a predetermined molecular weight profile could be synthesized by varying the time and temperature of the debenzylation reaction using the HBr in acetic acid. (Sept. Tr. (Sampson) 1641:18-1642:8; PTX 1, col. 4:48-col. 6:3.)

Dr. Sampson's testimony at trial, which this Court credits over Dr. Zeiger's testimony to the contrary, was that a person of skill in the art would not have been motivated to use HBr in acetic acid to cleave the peptide bonds in copolymer-1 polypeptides to

control the molecular weight of a copolymer-1 sample because the prior art as a whole taught that peptide bonds would not be cleaved during exposure to HBr/acetic acid. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1689:22-1690:11.) As Dr. Sampson explained, HBr/acetic acid was a standard deprotecting agent used during the synthesis of polypeptides. In those cases, cleavage of the polypeptide chain would need to be minimized or avoided altogether. One of ordinary skill attempting to make polypeptides would not have been motivated to use a reagent that would break polypeptides. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1655:13-1656:4; PTX 488.)

The two prior art references that mention the use of HBr/acetic acid during the synthesis of copolymer-1, the '550 patent and the 1971 Teitelbaum article, describe using HBr/acetic acid only for the purpose of debenzylation. (Sept. Trial Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26, col. 2:53-64; PTX 499 at 243.) Neither of these references mention peptide bond cleavage during the debenzylation step, nor do they mention the use of HBr in acetic acid to control the molecular weight of the resulting copolymer-1 product. (Sept. Trial Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26; PTX 499.)

Dr. Sampson testified that a person of ordinary skill in the art would have understood that the Weizmann scientists controlled molecular weight by adjusting the ratio of initiator to N-carboxyanhydrides of the respective amino acids during polymerization. (Sept. Trial Tr. (Sampson) 1652:12-1656:4; PTX 499; DTX 1783.)

Meanwhile, a well regarded and widely circulated 1963 paper by Nobel laureate Bruce Merrified stated that peptide bond cleavage would not occur upon exposure to Hbr/acetic acid. J. Am. Chem. Soc. , 85: 2149-54 (1963) ("Merrifield 1963"); (PTX 488.) Dr. Merrified had specifically investigated whether peptide cleavage took place after treatment with HBr/acetic acid in conditions similar to those described in the patents-in-suit (18 hours at 25 celcius) and he found no cleavage. (Sept. Trial Tr. (Sampson) 1644:20-1647:10; PTX 488 at 2151, 2153.)

Similarly, Yaron and Berger, "Multi-Chain Polyamino Acids Containing Glutamic Acid, Aspartic Acid and Proline," Biochimica et Biophysica Acta, 107: 307-332 (1965) ("Yaron & Berger 1965") (DTX 1934), reported that no cleavage of peptide bonds was detected when HBr/acetic acid was used for debenzylation carried out at 2 degrees for 3 days. (Sept. Trial Tr. (Sampson) 1650:7-1651:9; Sept. Trial Tr. (Zeiger) 851:9-853:3; 1685:13-22; PTX 1934.) The authors reported that under those conditions, they were able to obtain 100 percent deprotection of benzyl groups and avoid peptide bond cleavage. (Sept. Trial Tr. (Sampson) 1650:7-1651:9; 1685:13-22; Sept. Trial Tr. (Zeiger) 851:9-853:20; PTX 1934.)

Additionally, Yaron and Berger, "Multichain Polyamino Acids of Well Defined Degrees of Polymerization," Bulletin of the Research Counsel of Israel: Section A, Chemistry, 7A(2):96-97 (1958) ("Yaron & Berger 1958") (DTX 3233), investigated whether peptide bond cleavage occurred when HBr in acetic acid was used to deprotect benzyl groups during the synthesis of copolymers. The authors

concluded that "no degradation in the side chains occurred during debenzylation with HBr in glacial acetic acid at 2 degrees for three days." (Sept. Trial Tr. (Sampson) 1650:7-1651:9; Sept. Trial Tr. (Laird) 1146:9-1147:6.) As Dr. Sampson explained, this meant that no peptide bonds had been cleaved even after three days of exposure to HBr/acetic acid.

According to both Dr. Sampson and Sandoz's own expert Dr. Laird, the time and temperature of 2 degrees for three days reported in Yaron and Berger 1958 would be equivalent, through the application of a well-known chemical rule of thumb, to about 22-25 degrees for about 17-18 hours, conditions similar to those reported in the patents-in-suit. (Sept. Trial Tr. (Laird) 1146:9-1147:6; Sept. Trial Tr. (Sampson) 1650:7-1651:9, 1685:13-1686:18; PTX 1934 at 318; PTX 3233 at 97.) Since no cleavage was observed in the conditions used in Yaron and Berger 1958, one of ordinary skill in the art in 1994 would similarly expect that use of HBr in acetic acid for 17 hours at 25°C, as described in Example 4 of the patents-in-suit, would likewise result in no cleavage of peptide bonds. (Sept. Trial Tr. (Sampson) 1685:13-1686:18; DTX 1934 at 318.)

Two of the other prior art references relied on by the Defendants—the Katchalski and Sela reference and the Hayashi reference—discuss the use of HBr for debenzylation purposes in compounds other than copolymer-1, but they contain no independent or original observations concerning peptide bond cleavage. These references simply report discussion of suspected bond cleavage from earlier literature (Sept. Trial Tr. (Sampson) 1647:11-1648:10), and

neither mentions the use of HBr/acetic acid to control molecular weight. (See Sept. Trial (Sampson) 1647:25-1648:10, 1653:10-1655:8; Sept. Trial (Zeiger) 820:17-821:4; DTX 1781; DTX 1783.) Moreover, Hayashi 1985 does not even discuss the use of HBr in acetic acid. (Sept. Trial (Laird) 1150:16-1151:12; DTX 1781 at 464.)

The remaining prior art references relied on by the Defendants discuss possible peptide bond cleavage based upon an observed change in the molecular weight of a peptide after the use of HBr. These references—which include two papers published by Idelson and Blout in 1956 and 1958, and a reference by Appelquist and Doty published in 1962—contain no direct observation or testing to determine whether, in fact, peptide bond cleavage had occurred and whether HBr was responsible for such cleavage. (Sept. Trial Tr. (Sampson) 1648:11-1650:6; DTX 1934 at 317-318 n.21, 331 n.21; DTX 1855; DTX 1784.) At most, the Nylund and Miller 1965 reference states that "the degree of polymerization was always lowered during debenzylation [treatment with HBr in acetic acid]" and concludes that this result is due to "peptide bond cleavage by HBr . . . , thus broadening the molecular weight distribution." (DTX 1784 at 3541.)

iii. Secondary Considerations of Non-obviousness

Multiple sclerosis was first recognized as a distinct disease in the 1860s. (Sept. Tr. (Lisak) 88:8-89:18.) By the early 1990's, there was still no effective treatment that could slow the progress of the

disease. (Sept. Tr. (Lisak) 102:2-9, 131:14-136:19; PTX 523; PTX 538; PTX 565; PTX 591.) In 1994, the only disease-modifying treatment available for multiple sclerosis was Betaseron®, an interferon treatment that is ineffective in about 40% of multiple sclerosis patients and that causes significant side effects, including liver and bone marrow problems, depression, and a flu-like syndrome. (Sept. Tr. (Lisak) 125:25-126:3, 103:3-104:2, 104:11-105:18.)[34]

Copaxone®—Teva's copolymer-1 treatment for RRMS—was introduced in 1997. It works differently from interferon treatments and is able to effectively treat many of the patients for whom that treatment is ineffective. (Sept. Tr. (Lisak) 103:3-104:2, 118:9-119:7; 12 7:15-130:25; PTX 667, PTX 671; see also PTX 963 (B. Rao 9/30/2010 Dep.) at 226:23-228:13 (testifying that Copaxone® has "a better side-effect profile" and "a better therapeutic efficacy profile" as compared to the interferon treatments).)

Dr. Grant testified that, based on the data he had seen from Copaxone® certificates, analysis, and calculations, Copaxone® meets the average molecular weight, copolymer-1 molar fraction, and TFA-

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[34] Defendants argue that, as of 1986, copolymer-1 had been approved for treatment of patients with RRMS and adduced testimony at trial that in 1994, the need for an effective treatment for RRMS patients was therefore met by the copolymer 1 administered during the Bornstein clinical trial and approved by the FDA for administration to humans. (Sept. Tr. 1362:14-1368:19 (Green).) Because copolymer 1 was not brought to market until 1997, however, the Court finds that, regardless of the reason, there remained a need for effective multiple sclerosis treatments in 1994.

copolymer-1 limitations of the asserted claims. (PTX 105, PTX 349 at SDZ00017948-949; PTX 392 ; PTX 990 at "Copolymer-1 Molar Fraction Limitations-Copaxone" and "TFA Copolymer-1 Molar Fraction Values-Copaxone"; Sept. Tr. (Grant) 1468:5-1477:15.) Dr. Lisak's testimony at trial also demonstrates that Copaxone® meets the limitations related to treatment of multiple sclerosis. (Sept. Tr. (Lisak) 137:4-147:22; Sept. Tr. (Gokel) 1589; PTX 206; PTX 697; PTX 734.) Dr. Gokel further explained that Teva uses the same process steps that are in the patents-in-suit to make Copaxone®. (Sept. Tr. (Gokel) 1584:9-1590:20.)

Additionally, the testimony at trial was that annual sales of Copaxone® have grown nearly 100-fold from $25 million in 1997 to approximately $2.25 billion in 2010. (Sept. Tr. (Congleton) 49:8-12, 59:18-20.) Sales of Copaxone® in the United States have steadily grown and overtaken sales of its interferon competitors during this time and it has become the treatment of choice for RRMS by nearly a factor of two. (Sept. Tr. (Congleton) 50:12-51:2.) Since its introduction, total sales for Copaxone® have exceeded $10 billion, despite constant pressure from competitors. (Sept. Tr. (Congleton) 59:21-23, 66:6-7.) Approximately 100,000 patients are currently using Copaxone® to treat their multiple sclerosis. (Sept. Tr. (Congleton) 51:19-22.)

Dr. Lisak, Plaintiff's expert in multiple sclerosis and its treatment, (Sept. Tr. (Lisak) 87:24-88:6), explained that his Copaxone® prescriptions have increased over time because of its clinical advantages

over the competing treatments. (Sept. Tr. (Lisak) 119:8-120:9.)

Dr. Lisak's testimony at trial also discussed several failed attempts to develop multiple scelorsis treatments, including Isoprinisone and prednisone; immunosuppressant treatments such as Roquinimex, Gusperimus, Sulfasalazine, and Cladribine (a chemotherapy drug); cytokine modulators Lenercept, Infliximab, and TGF-32; antigen-derived therapies like oral bovine myelin and Tiplimotide; and monoclonal antibodies, including Muromonab-CD3, Priliximab, and Antova. (PTX 523; Sept. Tr. (Lisak) 132:18-24, 132:25-133:4; PTX 627; Sept. Tr. (Lisak) 133:5-7; PTX 591; Sept. Tr. (Lisak) 133:7-12; PTX 617; Sept. Tr. (Lisak) 133:23-134:6; PTX 623; Sept. Tr. (Lisak) 134:7-10; PTX 60; Sept. Tr. (Lisak) 134:11-14; PTX 6165; Sept. Tr. (Lisak) 134:15-21; PTX 644; Sept. Tr. (Lisak) 134:22-25; PTX 62; Sept. Tr. (Lisak) 135:3-8; PTX 565; Sept. Tr. (Lisak) 135:3-8; PTX 644; Sept. Tr. (Lisak) 135:9-13; PTX 99.)

iv. The Prior Art Does Not Teach Copolymer-1 Compositions with the Claimed Average Molecular Weight Characteristics

Defendants contend that the '550 Patent and the EP '620 Application were prior art suggesting that the claimed copolymer-1 compositions would have been obvious to a person of ordinary skill in the art.

The evidence does not support a conclusion that a person of ordinary skill would read the '550 patent to disclose copolymer-1 of 10,000 daltons and above.

While there is no dispute that the '550 patent, in column 1, uses the number 10,000 daltons, (Sept. Tr. (Grant) 1435:4-1437:19; Sept. Tr. (Zeiger) 930:4-931:23), there is insufficient evidence that a person of ordinary skill in the art would understand that molecular weight to apply particularly to copolymer-1 rather than to any of the other copolymers disclosed in the '550 patent.

As Dr. Grant explained, the '550 patent does not disclose copolymer-1 of 10,000 daltons. Rather, in Column 1, lines 57-68, the '550 patent generally discloses that copolymers can be in excess of 10,000 daltons and preferably above 18,000 daltons. (Sept. Tr. (Grant) 1435:2-1436:16; PTX 26, col. 1:57-68.) The patent then explicitly discloses an example of copolymer-1 between 20,000 and 25,000 daltons and claims copolymer-1 between 15,000 and 25,000 daltons. (Sept. Tr. (Grant) 1436:17-1437:19; PTX 26, col. 2:19-30, col. 3:24 col. 4:23; Sept. Tr. (Zeiger) 930:4-931:23.) Dr. Grant explained that a person of ordinary-skill in the art, reviewing this patent as a whole, would conclude that it disclosed copolymer-1 specifically only in the molecular weight range of 15,000 to 25,000 daltons. (Sept. Tr. (Grant) 1437:10-19.)

Defendants rely on Dr. Zeiger's testimony at trial. However, the testimony to which Defendants point actually supports Dr. Grant's reading of the '550 patent. Dr. Zeiger agreed that the reference in the '550 patent to "copolymers ... in excess of 10,000 daltons" was not a specific reference to copolymer-1. (Sept. Tr. (Zeiger) 932:9-12.) Dr. Zeiger further testified that the preferred molecular weight of the

copolymers discussed in column 1 of the '550 patent was "above 18,000 daltons," (Sept. Tr. (Zeiger) 840:16-18), but that the v550 patent taught that due to manufacturing variability, results might be as low as 10,000 daltons. (Sept. Tr. (Zeiger) 841:13-24.) Dr. Zeiger also explained that a person of ordinary skill would "shoot [] for" a molecular weight of 18,000 daltons, but might get a batch as low as "in excess of 10,000 daltons":

> Q. How does that person of ordinary skill in the art approach the disclosures of the process in the '550 patent to produce to the preferred range, what are the factors what does he look at?
>
> A. Well, the polymerization, as I mentioned, is going to give some batch-to-batch variability in terms of molecular weight. The fact that the preferred range is above 18,000 would indicate that that's what the patentees are shooting for, but nonetheless they fully acknowledge that they may get something as low as in excess of 10,000.

(Sept. Tr. (Zeiger) 843:9-18.) Dr. Zeiger thus agreed that the '550 patent teaches a person of ordinary skill in the art to target, or "shoot for" higher molecular weights. Lastly, Dr. Zeiger testified only generally about all of the "copolymers" disclosed in the '550 patent; he offered no testimony that the '550 patent as a whole would be interpreted to disclose copolymer-1 of 10,000 daltons. His testimony is therefore insufficient to prove, by clear and convincing evidence, that a person of ordinary skill

would interpret the '550 patent to disclose copolymer-1 of 10,000 daltons.

Like the '550 patent, the EP '620 Application does not disclose copolymer-1 compositions with an average molecular weight of about 5,000 to about 9,000 daltons. The EP '620 Application is not even directed to copolymer-1 compositions, as the term "copolymer-1" has been interpreted by the Court. (Sept. Tr. (Grant) 1445: 4--1447:-14; Sept. Tr. (Zeiger) 972:15-20; DTX 1970, p. 2, 11. 50-55, p. 11, 1.32-1.34.) Instead, the EP '620 Application is directed to discrete polypeptides made through recombinant DNA technology and identifies a preferred molecular weight for these individual polypeptides of 15,000 to 23,000 daltons. (Sept. Tr. (Grant) 1448:20-1449:19; Sept. Tr. (Zeiger) 972:15-20, 977:8-978:3; DTX 1970, p. 5, 11. 28-33.)

The Court therefore concludes that, based on the teachings of the '550 patent and the EP '620 Application, a person of ordinary skill in the art would have no reason to select or to make a copolymer-1 composition in the specific average molecular weight range of about 5 to 9 kilodaltons, or within the ranges of "about 4 to about 9 kilodaltons," or 6.25-8.4 kilodaltons.

This is consistent with Teitelbaum 1974, which expressly teaches away from copolymer-1 with an average molecular weight below 17,000 daltons, identifying such a composition as "ineffective" for the

treatment of EAE."[35] (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.)

v. There Is No "Overlap" in Average Molecular Weight Ranges or Molar Fraction Limitations

The Court rejects Defendants' argument that they have established prima facie obviousness by demonstrating "overlapping" molecular weight ranges between the claimed copolymer-1 compositions and the copolymer-1 compositions of the prior art.

Defendants' overlap theory is that the '550 patent disclosed copolymer-1 compositions with an average molecular weight of 10,000 daltons or above, which would have the same copolymer-1 polypeptides in almost the same amount as a composition of 5,000 to 9,000 daltons; therefore, a person of ordinary skill would have believed that a copolymer-1 composition with an average molecular weight of about 5,000 to 9,000 daltons would have the same properties as a copolymer-1 composition of 10,000 daltons or above.

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[35] Defendants refer to Bornstein 1987 as a piece of art that post-dates Teitelbaum 1974 and establishes that compositions as low as 14,000 daltons were clinically safe and effective. (PTX-31 at 408.) Notwithstanding that teaching, in view of the prior art as a whole, the Court finds that it does not suggest any reason that a person of ordinary skill would change, adjust or lower the average molecular weight of copolymer-1 to the claimed ranges.

In the first instance, as stated above, the Court does not find that the '550 Patent taught a copolymer-1 composition having an "average molecular weight" of 10,000 daltons. Therefore, the average molecular weight ranges disclosed in the relevant prior art—the '550 Patent—do not overlap with any of the claimed ranges.

Even if the '550 patent taught a copolymer-1 composition with an average molecular weight of 10,000 daltons, which it does not, that composition does not overlap with a peak average molecular weight range of 5-9 kilodaltons, about 4-9 kilodaltons or 6.25-8.4 kilodaltons.

In order for an overlap claim to succeed, the prior art must disclose a range that overlaps a claimed range. Lazare Kaplan Int'l, Inc. v. Photoscribe Techs., Inc., 628 F.3d 1359, 1380-81 (Fed. Cir. 2010) ("[A] prior art reference that discloses a range that encompasses or overlaps a claimed range generally is sufficient to establish a prima facie case of invalidity.") (emphases added). So here, where the claims are directed to an average molecular weight, Defendants must establish that the prior art discloses an average molecular weight that overlaps with the claimed range. See In re Huai-Hung Kao, 639 F.3d 1057, 1066-67 (Fed. Cir. 2011) (requiring that "the claimed range of dissolution rates actually overlaps with the dissolution rate disclosed in [prior art reference]"); In re Kumar, 418 F.3d 1361, 1364 (Fed. Cir. 2005) (analyzing overlap issues for claim directed to average particle size by analyzing the average particle size of the prior art).

Dr. Zeiger admitted during cross examination that there is no overlap between the claimed average molecular weights (i.e., peak molecular weights) and the average molecular weight disclosed in the '550 patent (even with his interpretation of the '550 patent as disclosing copolymer-1 with an average molecular weight of 10,000 daltons). (Sept. Tr. (Zeiger) 938:11-15; 941:8-16.)

Accordingly, with respect to all of the claims directed to average molecular weights, Defendants have not shown an overlap.

Nor is there evidence of any overlap between the prior art and the claimed molar fraction ranges. Those claim limitations require, for example, that more than 75% of the molar fraction of copolymer-1 molecules have a molecular weight between 2,000 and 20,000 daltons or that less than 5% of the molar fraction of copolymer-1 molecules have a molecular weight above 40,000 daltons. (PTX 4, col. 5: 21-col. 6:8; PTX 9, col. 5:41-50.) To establish an overlap on that claim element, then, Defendants must identify a prior art disclosure of a molar fraction of copolymer-1 that overlaps or encompasses the claimed molar fraction ranges, i.e., a prior art reference disclosing percentages of copolymer-1 polypeptide species between 2,000 and 20,000 daltons in a range that overlaps with the range of "more than 75%."

Defendants have not presented reliable evidence to establish such overlap. Defendants only asked Dr. Zeiger to state whether he would expect a person of ordinary skill in the art to believe that there was a "high" percentage of species between 2,000 and

20,000 daltons for a batch of copolymer-1 with an average molecular weight between 10,000 and 15,000 daltons. (See, e.g., (Sept. Tr. 987:8-12 (Zeiger).) That testimony does not establish what percentage of copolymer-1 molecules, on a molar fraction basis, have molecular weights between 2,000 to 20,000 daltons.

To compensate for its lack of evidence of overlap, Mylan attempts to rely on the law of inherency. In this regard, Mylan claims that it is inherent in the compositions' properties that copolymer-1 batches having similar average molecular weights would have had substantial overlap in their molecular weight profiles. It argues that such "inherent properties" are, as a matter of law, considered part of the prior art and therefore within the general knowledge of a person of ordinary skill in the art.

The Court rejects this argument as it is unsupported by the evidence. For one, Mylan has not presented any evidence that the molecular weight distribution of every batch of copolymer-1 made pursuant to the prior art would have the purported overlap, or even that copolymer-1 would have an "inherent" molecular weight distribution.

Moreover, no molar fraction data can be derived from the '550 patent. To determine what percentage of species falls within a particular range requires knowing the overall distribution of all the species in the sample. (See Sept. Tr. (Grant) 228:12-230:7.) But, as Dr. Zeiger admitted, there is no disclosure in the '550 patent of (i) the molar fractions of any type of molecule, (ii) a molecular weight distribution for any

copolymer, or (iii) data from which one could calculate the molar fractions for a copolymer-1 sample. (Sept. Tr. (Zeiger) 956:10-957:13.) Accordingly, the '550 patent cannot disclose an overlapping range for any molar fraction claim limitation.

At most, Mylan presented evidence of a limited number of examples in which the molecular weight distribution of samples of copolymer-1 made pursuant to the disclosure of the '550 patent yields a large percentage of species between 2,000 and 20,000 daltons. (Sept. Tr. 879:1-16 (Zeiger); DTX-1704-R at TEV003004347; Sept. Tr. 905:17-21 (Zeiger); DTX-1704-Rat TEV003004349.) Such examples (even if correctly characterized) do not establish that every batch of copolymer-1 made pursuant to the processes disclosed in the '550 patent would have greater than 75% of its copolymer-1 molecules, on a molar fraction basis, having molecular weights between 2,000 and 20,000 daltons.

To establish inherency, Mylan must prove that an attribute is necessarily present each time the prior art is practiced. See Trintec Indus., Inc. v. Top-U.S.A. Corp., 295 F.3d 1292, 1295 (Fed. Cir. 2002) ("Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art."). Against this standard, citing a few examples where overlap might occur is legally insufficient to establish that the claimed molar fractions inherently overlap with the molar fractions of the prior art. See also Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043, 1047-48 (Fed. Cir. 1995) (holding no inherent

disclosure of claimed crystalline polymorph by prior art patent where practicing disclosed prior art method could produce claimed polymorph or alternative unclaimed polymorph); W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1554 (Fed. Cir. 1983) ("Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references.").

vi. The Defendants Have Not Demonstrated Evidence of Any Reason or Motive to Alter the Molecular Weight of Copolymer-1

Even if Defendants had established an overlapping range, in order to establish a prima facie case based on such theory in the context of this case, Defendants would additionally need to demonstrate a reason for a person of ordinary skill in the art to change the molecular weight of copolymer-1 to the claimed ranges. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 418 (2007) (confirming that it remains "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does, [as] most, if not all, instances rely upon building blocks long since unconvered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known"); Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc., 655 F.3d 1291, 1304 (Fed. Cir. 2011).

Here, as in Genetics Inst., LLC, in the field of the patents-in-suit, it cannot be said that a person of ordinary-skill in the art would arrive at the invention by the standard course of optimizing variables within a claimed range. Id. at *1305-06 (noting that despite some overlap, "the nontrivial differences in the proteins at issue compel the requirement of identifying a reason for the chemical modification"). Rather, in the field at issue, there is a broad range disclosed in the prior art and, accordingly, there must be a reason identified as to why a person of ordinary skill would select a lower average molecular weight or the claimed molar fractions.

Mylan's cited testimony supports no such conclusion. Mylan relies upon Dr. Zeiger, who testified:

> Q. And what would the person of ordinary skill have expected in 1994 concerning the chemical and biological properties of two batches of copolymer-1 that had substantial overlap in their molecular weight profiles?
>
> A. I would have expected him to perhaps anticipate with an overwhelming or an extremely large percent of sizes in common, that there would be similar biological properties. This is clearly not a one-on-one absolute kind of level, but I would have expected him to anticipate this.

(Sept. Tr. (Zeiger) 873:2-10).) This testimony, unsupported by any citation to a publication or prior

art, cannot carry the Defendants' burden on this issue.

There is no other testimony that there would necessarily be an "overwhelming" or "extremely large" overlap of species, or even an explanation of what that means.

Mylan also relies on Dr. Rice's testimony that it was known that changing molecular weight can influence toxicity. However, Dr. Rice admitted during cross-examination that a person of ordinary skill would not have an expectation whether toxicity would increase or decrease by varying molecular weight, only that it could change. (Sept. Tr. (Rice) 1047:14-1048:6.)

The Court therefore concludes that the testimony at trial does not provide clear and convincing proof that a person of ordinary skill would have been motivated to create copolymer-1 in the claimed ranges.

vii. The Claimed Ranges Do Not "Abut" the Prior Art

Defendants also argue that, even if the molecular weight ranges of the prior art do not overlap with the claimed ranges, they are sufficiently close or "abutting" such that the Court should find prima facie obviousness on this basis alone.

Even if the '550 Patent discloses a peak average molecular weight of 10 kilodaltons—and the Court has found that it does not—the "average molecular

weight" ranges of the claims and the '550 patent do not "abut" a range of "about 5 to 9 kilodaltons," "about 4 to about 9 kilodaltons" or "6.25-8.4 kilodaltons." With respect to the peak average molecular weight ranges, in order to abut, prior art and claimed ranges must literally touch. See e.g., In re Woodruff, 919 F.2d 1575, 1576, 1578 (Fed. Cir. 1990) (disclosed range of "about 5%" abutted claimed range of "more than 5%").

A court will only find prima facie obviousness in this context if the ranges are so close that a person of ordinary skill in the art would expect that the properties of such different compounds would be the same. See Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 783 (Fed. Cir. 1985) (finding ranges to be close because a person of ordinary skill would expect similar properties).

Here, Defendants have presented no evidence that a person of ordinary skill would expect the properties of compounds with different molecular weights to be the same. Mylan's analysis of what a person of ordinary skill in the art would expect is grounded on an analysis of documents that Mylan admits are not prior art. (Sept. Tr. (Zeiger) 941:17-944:1, 945:6-12.) The Court finds that Dr. Zeiger's testimony, recounted above, concerning the overlap of species within a copolymer-1 mixture, are irrelevant to the question of whether a person of ordinary skill would consider the molecular weight disclosure of the '550 patent close to, or abutting, the claimed ranges and does not establish that a person of skill would expect similar biological properties between the claimed weight ranges and those in the prior art. And Dr.

Zeiger's unsupported speculation that a person of skill might "perhaps anticipate" similar biological properties is insufficient to carry Defendants' clear and convincing burden of proof. See Star Scientific, Inc., 655 F.3d at 1376 (a prior art reference's "speculative and tentative disclosure of what 'might' or 'may' [happen] does not sufficiently direct or instruct one of skill in th[e] art").

With respect to the molar fraction limitations, as stated, the Court finds that there is no explicit or inherent molar fraction in the prior art. Accordingly, it is impossible to establish any relationship, whether overlapping, abutting or otherwise, of the claimed molar fraction attribute and the prior art.

Nor can the EP '620 Application support an "abutting" range theory because, again, it discloses neither copolymer-1 nor an average molecular weight for copolymer-1. (Sept. Tr. (Grant) 1444:13-1448:16; Sept Tr. (Zeiger) 884:23-885:4, 972:15-20, 975:9-23, 976:15-23; DTX 1970, p.2, 1. 50.)

viii. The Prior Art "Taught Away" from Molecular Weights in the Claimed Ranges

Even if Defendants had established a prima facie case of obviousness based on a theory of overlapping or abutting ranges, which the Court does not find, Plaintiff has rebutted such case by showing that the prior art taught away from the invention. See Iron Grip Barbell Co. v. USA Sports Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004).

Teitelbaum 1974 explicitly taught away from copolymer-1 with an average molecular weight below 17,000 daltons, calling them ineffective for treatment of EAE. (July Tr. (Arnon) 312:23-313:18; Sept. Tr. (Grant) 1442:8-1444:9; PTX 509 at 1172-1173.) And, as described, the '550 Patent and the EP '620 Application expressed preferences for higher molecular weights.

Defendants point to the Bornstein studies and Bornstein 1987 which, they claim, taught that having an average molecular weight as low as 14,000 daltons was safe and effective. (PTX-31 at 408, 413-414.) However, Defendants do not offer any explanation of why, notwithstanding the Bornstein research, a person of ordinary skill in the art would believe that copolymer-1 of 5-9 kilodaltons would be active in light of the clear teaching away in Teitelbaum 1974 and the preferences for higher weight copolymer expressed in the '550 Patent and the EP '620 Application.

ix. The Claimed Weight Characteristics of the Patents-in-Suit Are Not Obvious

Because a person of ordinary skill in the art would not have found obvious a copolymer-1 having the claimed average molecular weight or molar fraction limitations, Defendants have failed to prove by clear and convincing evidence that the following claims are invalid for obviousness: claim 1 of the '808 patent, claim 1 of the '589 patent, claims 1 and 6 of the '847 patent, claims 1-3 of the '430 patent, claim 1 of the '476 patent, claim 1 of the '161 patent, claims 1

and 8 of the '098 patent, and claims 1, 8, 9, 10, 12, 23, 30, and 31 of the '539 patent.[36]

Claims 1-3 of the '898 patent are not addressed to a specific numerical limitation on the molecular weight of copolymer 1, but rather require a "predetermined molecular weight profile." However, because Defendants have not presented evidence of any reason or motive for a person of ordinary skill in the art to adjust the weight of copolymer-1 to the predetermined molecular weight in those claims, they have not demonstrated by clear and convincing evidence that they are prima facie obvious either. See KSR Int'l Co., 550 U.S. at 418-19.[37]

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[36] The Court rejects Defendants' argument of judicial estoppel, which they raised post trial. The Defendants essentially argue that Teva admitted during the prosecution of the asserted patents that the '550 Patent teaches copolymer 1 of 10 kilodaltons, and so Teva is now estopped from arguing that a molecular weight of 10 kilodaltons is not in the prior art.

"Judicial estoppel applies when a party takes a later position that is inconsistent with a former position in the same dispute, on which the party had been successful and had prevailed based on the former position." Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp., 523 F.3d 1304, 1315 (Fed. Cir. 2008) (citation omitted). "Judicial estoppel is an equitable doctrine invoked by a court at its discretion." Cacace v. Meyer Mktg. (Macau Commer. Offshore) Co., 812 F. Supp. 2d 547, 564 n.17 (S.D.N.Y. 2011) (citation omitted) The Court finds that Defendants have failed to satisfy multiple prongs of the judicial estoppel doctrine, and therefore will not, in its discretion, invoke that doctrine.

[37] The Court also rejects Defendants' attempt to establish a prima facie case of obviousness based on "structural similarity" in chemical structures and properties between the prior art and the claimed compounds. To establish obviousness of a chemical compound, the Federal Circuit now requires that a defendant

x. The Claimed Process for Making Copolymer-1 in HBr/Acetic Acid Is Not Obvious

Even if Defendants had proven by clear and convincing evidence that a person of ordinary skill in the art would have tried to make a copolymer-1 with the claimed average molecular weights or molecular weight molar fractions, there is nothing to suggest that such person would have attempted to use HBr in acetic acid to achieve that molecular weight or molar fraction.

The only two references that Drs. Zeiger and Laird introduced regarding the use of HBr in acetic acid for synthesizing copolymer-1 were the '550 patent and the Teitelbaum 1971 article. But neither of these references mention peptide cleavage during the debenzylation step, nor do they mention the use of HBr in acetic acid to control the molecular weight of the resulting copolymer-1 product. (Sept. Tr. (Sampson) 1651:20-1652:11, 1653:4-1655:12; PTX 26, col. 2 11.53-64; PTX 499 at 243.)

Dr. Zeiger, Mylan's expert, testified that the person of ordinary skill in the art would find references suggesting possible cleavage of peptide bonds following the use of HBr in acetic acid by following a "trail" of six references: (i) the

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identify a "lead compound," that is, a compound with which a person of ordinary skill would start the analysis. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 45 (Fed. Cir. 2000); Takeda Chern. Indus., Ltd., 492 F.3d at 1357-60. Here, Defendants have failed to identify any such compound; therefore, their argument fails.

'550 patent; (ii) Teitelbaum 1971; (iii) Ben-Ishai and Berger; (iv) Yaron and Berger; (v) Idelson and Blout; and (vi) Nylund and Miller. (Sept. Tr. (Zeiger) 817:19-818:17, 826:25-827:22, 945:14-952:15, 951:23-952:15.) However, this trail includes no prior art publication explaining that the amount of cleavage of a peptide bond could be controlled such that a "predetermined molecular weight profile" could be achieved by using HBr/acetic acid.

There was no evidence to show that a person of skill in the art would have been motivated to try to control peptide cleavage by changing the time and temperature of the reaction. The opinions of Defendants' experts are based on hindsight. Dr. Laird and Dr. Zeiger cite to references reporting that the use of HBr in acetic acid for debenzylation could potentially result in some peptide cleavage. (Sept. Tr. (Laird) 1139:10-1142:9; (Sept. Tr. (Zeiger) 859:22-860:5.).) But neither Dr. Laird nor Dr. Zeiger offered any explanation why the person of ordinary skill in the art would seek to use the debenzylation reaction, or HBr in acetic acid, to cleave the peptides during the process for making copolymer-1 in view of the prior art. (Sept. Tr. (Laird) 1155:4-23; Sept. Tr. (Zeiger) 817:19-818:17, 945:14-952 :15.)

Rather, the evidence shows that a person of skill in the art would not have been motivated to use HBr in acetic acid to cleave the peptide bonds in copolymer-1 polypeptides in order to control the molecular weight of a copolymer-1 sample. As previously noted, Dr. Sampson testified that HBr in acetic acid was used as a step in the synthesis of polypeptides, where the cleavage of the polypeptide chain would be viewed

negatively, as something that would need to be minimized or avoided altogether. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1655:13-1656:17, 1683:16-19; PTX 488.) That testimony is consistent with the prior art relied on by Defendants, which shows that the alleged cleavage disclosed was, at best, an undesirable side reaction, not something that would be viewed as a tool to be used to decrease the molecular weight of copolymer-1. (Sept. Tr. (Sampson) 1642:9-20, 1655:13-1656:4; Sept. Tr. (Laird) 113 9:22-1140:8; 1154: 2 -1155:12.)

Moreover, as explained in detail by Dr. Sampson, Merrifield's 1963 paper carefully considered and studied whether HBr/acetic acid, under conditions similar to those disclosed in the patents-in-suit, would cleave peptide bonds. Merrifield concluded that it would not. (Sept. Tr. (Sampson) 1644:20-1647:10; PTX 488 at 2151, 2153.) Dr. Zeiger's testimony that the person of ordinary skill in the art would ignore the Merrifield 1963 article because it did not directly address whether HBr in acetic acid could cleave a specific type of peptide a gamma-benzyl glutamic acid containing peptide is not credible. That testimony is directly refuted by the testimony of Dr. Laird that the person of ordinary skill in the art would not focus on benzyl containing peptide bonds because all peptide bonds are closely similar. (Sept. Tr. (Laird) 1151:18-25.) Moreover, Dr. Zeiger's focus on gamma-benzyl glutamic acid containing peptides is based on hindsight. Dr. Zeiger did not provide any reason why a person of ordinary skill in the art would conclude that gamma-benzyl glutamic acid bonds is the site of cleavage in protected copolymer-1 polypeptides treated with HBr

in acetic acid, nor did Dr. Zeiger identify any reason that a person of skill in the art would have focused on the gamma-benzyl glutamic acid bond other than the fact that it is found in copolymer-1.

In view of the prior art as a whole, the Court concludes that Defendants have failed to establish that there would have been any motivation to adjust the molecular weight of copolymer-1, or that it would have been obvious to do so through the use of the HBr/acetic acid step. Therefore, the Court concludes that Defendants have failed to prove that the use of Hydrobromic (HBr) acid in acetic acid to cleave peptide bonds in order to control molecular weight would have been obvious to a person of ordinary skill in the art in May 1994. While it was known in the art that HBr in acetic acid could be used for debenzylation, a reaction to remove the benzyl protecting group from an amino acid, such as glutamic acid, there was no prior art disclosure that this reagent could also depolymerize polypeptides to control the average molecular weight.

Certain asserted claims of the patents-in-suit include specific time and temperature limitations. Those include claims 2 and 3 of the '898 patent and claims 2 and 3 of the '430 patent. Defendants have also failed to prove that the person of ordinary skill in the art would have been motivated to select or would have selected any particular time and temperature for the HBr/acetic acid step or that a person of ordinary skill in the art would have had any expectation that selecting a particular time and temperature for performing the HBr in acetic acid deprotection reaction would affect the resulting

average molecular weight or molar fractions of the copolymer-1 product. (Sept. Tr. (Sampson) 1644:20-1647:10; 1685:13-1686:18; PTX 488 at 2151, 2153; DTX 1934 at 318.)[38] Thus, Defendants have also failed to establish that the person of ordinary skill in the art would have selected a time of 10-50 hours and a temperature of 20-28°C or a time of about 17 hours and a temperature of about 26°C for the reaction of protected copolymer-1 with HBr in acetic acid, as recited in claims 2 and 3 of the '898 patent and claims 2 and 3 of the 4430 patent. Defendants have therefore failed to demonstrate the obviousness of these claims by clear and convincing evidence.

Claims 1-3 of the '898 patent, which require obtaining a "predetermined molecular weight profile" through the use of HBr in acetic acid would similarly not have been obvious. Defendants have not established by clear and convincing evidence that a

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[38] The Court does not believe that Defendants have proven by clear and convincing evidence that it would have been obvious to a person of ordinary skill in the art in May 1994 to select the recited time and temperature conditions to arrive at a particular average molecular weight or molar fraction of copolymer-1 during a process of routine optimization or experimentation of two common chemical reaction variables. Defendants' arguments in this regard are based on hindsight and are rejected. As set forth in detail above, a person of ordinary skill in the art would have had no reason to vary the molecular weight profile of copolymer-1. Moreover, the prior art achieved the higher disclosed molecular weight without using the HBr/acetic acid step to control or adjust the molecular weight. (Sept. Tr. (Sampson) 1642:9-1643:6, 1646:22-1647:10, 1652:12-1656:17, 1689:22-1690:11.) Defendants thus identified no reason a person of ordinary skill in the art would affirmatively use HBr/acetic acid to control or adjust the molecular weight of copolymer-1.

person of ordinary skill would have been motivated to set a predetermined molecular weight profile for copolymer-1 or that it would have been obvious that such a molecular weight profile could be controllably achieved through treatment of protected copolymer-1 with HBr in acetic acid.

xi. Secondary Considerations of Non-obviousness

There are also secondary considerations that support the Court's conclusion that the asserted claims are not obvious. Secondary considerations "may often be the most probative and cogent evidence [of non-obviousness] in the record." Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983).

1) Commercial Success

The commercial success of an embodiment of the claimed invention is strong evidence of its non-obviousness. See Graham v. John Deere Co., 383 U.S. 1, 17 (1966); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957 (Fed. Cir. 1997) (evidence of commercial success may be "highly probative of the issue of nonobviousness"). To establish commercial success, a patentee must show significant sales in the relevant market and a nexus to the claimed invention (that the success was due to the patented invention). Rolls-Royce, PLC v. United Tech. Corp., 603 F.3d 1325, 1340 (Fed. Cir. 2010).

"[I]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus

is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." Brown & Williamson Tobacco Corp. v. Phillip Morris, Inc., 229 F.3d 1120, 1130 (Fed. Cir. 2000). A successful product is "coextensive" with the claimed invention when it is commensurate in scope with the patented invention, as opposed to only a "component of a commercially successful" product. Mitsubishi Chem. Corp., 718 F. Supp. 2d at 436, 437 (finding a pharmaceutical formulation "coextensive" with the asserted claims where it was an "inextricable and essential part of what doctors are prescribing" and "not a part that can be separated out from the remainder of the product").

As described above, sales of Copaxone® in the United States have steadily grown and overtaken sales of its competitors such that it is now the treatment of choice by nearly a factor of two. Since its introduction, total sales for Copaxone® have exceeded $10 billion, despite constant pressure from competitors.

There is a nexus between Copaxone® and the claimed invention—Copaxone® is coextensive with the asserted claims, as the claimed invention is "an inextricable and essential part of what doctors are prescribing" when they prescribe the product. See Id. at 437.

Defendants have failed to present any evidence that Copaxone®'s success was related in any way to extraneous factors such as marketing or advertising, or due to features known in the prior art. In the absence of such evidence, Defendants have failed to

rebut the presumed nexus. Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1378 (Fed. Cir. 2000); Brown & Williamson Tobacco Corp., 229 F.3d at 1130 ("The presumed nexus cannot be rebutted with mere argument; evidence must be put forth."); Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1393 (Fed. Cir. 1988) ("[I]t is thus the task of the challenger to adduce evidence to show that the commercial success was due to extraneous factors .. [A]rgument and conjecture are insufficient." (internal quotation marks and citation omitted)).

Therefore, the Court concludes that Copaxone® is a commercial success, which finding supports its conclusion that the asserted claims were not obvious.

2) Long-felt, Unmet Need

"Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness." In re Dow Chem. Co., 837 F.2d 469, 472 (Fed. Cir. 1998) (citation omitted). "The existence of an enduring, unmet need is strong evidence that the invention is novel, not obvious, and not anticipated. If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence—the kind that can't be bought from a hired expert, the kind that does not depend on fallible memories or doubtful inferences—of the state of knowledge." In re Manhurkar Double Lumen Hemodialysis Catheter Patent Litig., 831 F. Supp. 1354, 1378 (N.D. 111. 1993), aff'd, 71 F.3d 1573 (Fed. Cir. 1995). Where there is a long-standing need in the medical community for a safe and

effective treatment for a particular disease, an invention that fulfills that need is often deemed non-obvious. See Eli Lilly & Co. v. Zenith Goldline Pharmas., Inc., 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("The record shows a long-felt need for a safer, less toxic, and more effective clozapine-like drug."); Pfizer, Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 518 (D. Del. 2005) (finding that, despite other products available on the market, "Lipitor® satisfied a long-felt need in the medical community to provide patients with more effective statins to help them achieve their LDL goals"), rev'd on other grounds, 457 F.3d 1284 (Fed. Cir. 2006).

The facts show that by 1994, there remained a long, unmet need for an effective, safe, and tolerable disease-modifying treatment for RRMS. (Sept. Tr. (Lisak) 125:25-127:14.) The introduction of Copaxone® thus fulfilled long-felt, unmet needs for: (a) an additional effective, safe, and tolerable treatment for RRMS; (b) a treatment for RRMS with a unique mechanism of action that worked differently than interferons; and (c) a treatment that had a milder side effect profile than the interferons. (Sept. Tr. (Lisak) 125:25-128:25.) Copaxone®'s fulfillment of each of these long-felt needs are secondary considerations that further support a finding of non-obviousness concerning the asserted claims of the patents-in-suit. See Eli Lilly & Co, 471 F.3d at 1380 (Fed. Cir. 2006); Pfizer, Inc., 405 F Supp. 2d at 518.

3) Failure of Others

The repeated failure of others to solve a problem addressed by an invention is further confirmation of the invention's non-obviousness. See Graham, 383 U.S. at 17 (noting that the "failure of others" is a secondary consideration of non-obviousness). In the pharmaceutical industry, the failure of others to develop a safe and effective drug often supports the non-obviousness of a drug that finally achieves success. See, e.g., Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 21 F. Supp. 2d 366, 374 (S.D.N.Y. 1998), aff'd, 231 F.3d 1339 (Fed. Cir. 2000) (stating that the evidence showing that "the pharmaceutical industry at large was attempting to improve upon existing [anti-ulcer drugs] with only a small number of producers coming close to success" supports a finding of non-obviousness) ; Eli Lilly & Co. v. Zenith Goldline Pharm., 364 F Supp. 2d 820, 832 (S.D. Ind. 2005), aff'd, 471 F 3d 1369 (Fed. Cir. 2006).

Evidence was presented at trial of drugs that showed initial promise for the treatment of multiple sclerosis, but that failed because of lack of efficacy or significant side effects. (Sept. Tr. (Lisak) 131:14-136:19; PTX 99; PTX 523; PTX 538; PTX 591; PTX 605; PTX 616; PTX 617; PTX 623; PTX 626; PTX 627; PTX 644.) The patents-in-suit are directed to the problem of developing an effective, safe, and tolerable treatment for multiple sclerosis. Each of the failed attempted therapies were similarly aimed at finding an effective, safe, and tolerable treatment for multiple sclerosis. Copaxone®'s success in light of these failed attempts provides further confirmation

of the non-obviousness of the asserted claims. See Yamanouchi Pharm. Co., 21 F Supp. 2d at 374; Eli Lilly & Co., 364 F. Supp. at 832; see also Uniroyal, Inc., 837 F.2d at 1054 (recognizing the "well established principle that the failure of others to provide a feasible solution to a long standing problem is probative of nonobviousness") (citation omitted).

4) Unexpected Results

Unexpected superior properties or advantages of an invention also indicate non-obviousness. Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 993 (Fed. Cir. 2009). As the Federal Circuit has explained, "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (citation omitted). Unexpected results may be shown with proof that (1) there is a difference between the results obtained and the closest prior art, and (2) the differences would not have been expected by one skilled in the art at the time of the invention. Procter & Gamble Co., 566 F.3d at 997-98.

The unexpected reduced toxicity of a drug as tested on animal models supports a finding of non-obviousness. See, e.g., Procter & Gamble Co. v. Teva Pharms. USA, Inc., 536 F Supp. 2d 476, 487-88, 495-96 (D. Del. 2008) (unexpected reduced toxicity demonstrated using a "short term toxicity screen" with rats), aff'd, 566 F.3d 989 (Fed. Cir. 2009); Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 417 F. Supp. 2d 341, 357-58, 385-86 (S.D.N.Y. 2006)

(unexpected lower toxicity demonstrated in mice and rat testing, as well as an in vitro chick lens assay).

The record establishes that low molecular weight copolymer-1 was unexpectedly superior to the prior art copolymer-1. The in vivo and in vitro toxicity data generated by the Weizmann scientists and Teva showed that the claimed lower molecular weight copolymer-1 had unexpectedly lower toxicity than higher molecular weight copolymer-1 batches. (See, e.g., July Tr. (Arnon) 333:18-334:2; July Tr. (Pinchasi) 32:1-6, 33:6-35:5, 46:21-47:8, 48:4-49:11, 55:7-58:21, 59:1-70:11; PTX 54; PTX 53; PTX 40.) Dr. Baird considered these and other data, and explained that they established a trend of decreasing toxicity with decreasing molecular weight. (July Tr. (Baird) 603:20-605:18, 607:10-608:15; PTX 34T; PTX54; PTX 887 at 44.) Dr. Pinchasi also described the existence of this trend and stated that the relationship between molecular weight and toxicity was "very unexpected" since nothing in the literature pointed the development team in that direction. (July Tr. (Pinchasi) 32:1-6.) Defendants' toxicology expert, Dr. Susan Rice, agreed that one of skill in the art would have no expectation with respect to how lowering the molecular weight of copolymer-1 would impact toxicity. (Sept. Tr. (Rice) 1046 -.25-1047:7.)[39]

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[39] The court discounts Dr. Rice's testimony that the entirety of toxicity data does not evidence unexpected results, as Dr. Rice failed to consider all the data, and instead based her opinion solely on what was presented in the patent specification and in the April 1994 Data Table. (See Sept. Tr. (Rice) 1042: 12 1043:1.)

The Court accepts this testimony as evidence of unexpected results. See, e.g., Merck Sharp & Dohme Pharms., SRL v. Teva Pharms. USA, Inc., No. 07-1596, 2009 WL 3153316, at *17, *52 (D.N.J. Aug. 19, 2009) (scientists involved in the development of montelukast found the compound to be surprisingly effective); W.R. Grace & Co.-Conn. v. InterCat, Inc., 7 F. Supp. 2d 425, 463-64 (D. Del. 1997), aff'd, 155 F.3d 572 (Fed. Cir. 1998) (activity of a composition "was a complete surprise" to inventors and others involved in the development). The lower toxicity of the low molecular weight copolymer-1 is thus an unexpected result that provides further support for a finding of non-obviousness regarding the asserted claims. See Procter & Gamble Co., 536 F. Supp. 2d at 487-88; Takeda Chem. Indus., Ltd., 417 F. Supp. 2d at 357-58, 385-86.

5) Copying

Even though Defendants are ANDA filers, their deliberate copying of the inventions provides additional evidence of non-obviousness. DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1328-29 (Fed. Cir. 2009); Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1285-86 (Fed. Cir. 2000). "The fact that copying is likely to be present in many Hatch-Waxman Act cases does not allow the court to ignore the copying as evidence of nonobviousness" and, in fact, in the field of new drug design, "the very need for copying results from and emphasizes the unpredictability of medicinal chemistry." Eli Lilly & Co. v. Zenith Goldline Pharms., No. IP 99-38, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001); see also Sanofi-

Aventis Deutschland GmbH v. Glenmark Pharms., Inc., No. 07-CV-5855, 2011 WL 383861, at *9 (D.N.J. Feb. 3, 2011) ("Copying, as secondary considerations evincing non-obviousness, is [an] important part of demonstrating non-obviousness even in a pharmaceutical patent case against an ANDA filer because an ANDA filer is not required to copy.") (emphasis in original).

Both Sandoz and Mylan attempted to develop alternative processes to manufacture copolymer-1 without infringing claims of the patents-in-suit, but both ultimately settled on following the claimed methods. (PTX 966 (Ray Dep.) at 78:8-84:10, 112:3-119:5; PTX 963 (B. Rao 9/30/2010 Dep.) at 39:25-44:2.)

This evidence of copying further supports a finding that the claims of the patents-in-suit are not obvious.

The Court has considered all of the Defendants' remaining arguments and has found them to be without merit.

CONCLUSION

For the reasons provided above, the Court finds that both Mylan's and Sandoz's ANDA infringe all of the asserted claims, and that none of the asserted claims are invalid or unenforceable.

Teva is ordered to submit a proposed judgment incorporating the rulings contained in this Opinion and Order to the Court on or before July 2, 2012.

SO ORDERED:

Barbara S. Jones

BARBARA S. JONES
UNITED STATES DISTRICT JUDGE

Dated: New York, New York
June 22, 2012

No. 13-854

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

JOINT APPENDIX, VOL. V (pp. 1138a-1358a)

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PETITION FOR A WRIT OF CERTIORARI FILED JANUARY 16, 2014
CERTIORARI GRANTED MARCH 31, 2014

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US005800808A

United States Patent [19]

Konfino et al.

[11] Patent Number: 5,800,808

[45] Date of Patent: Sep. 1, 1998

[54] **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

[75] Inventors: **Eliezer Konfino**, Ramat Gan; **Michael Sela**, Rehovot; **Dvora Teitelbaum**, Rehovot; **Ruth Arnon**, Rehovot, all of Israel

[73] Assignee: **Veda Research and Development Co., Ltd.**, Rehovot, Israel

[21] Appl. No.: **647,146**

[22] Filed: **May 22, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 344,248, Nov. 23, 1994, abandoned, which is a continuation of Ser. No. 248,037, May 24, 1994, abandoned.

[51] Int. Cl.[6] **A61K 27/00**

[52] U.S. Cl. **424/78.08**; 424/78.26; 424/78.29; 514/561; 525/420; 525/434; 525/435; 528/328

[58] Field of Search 424/78.29, 78.08, 424/78.26; 514/561; 525/420, 434, 435; 528/328

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(List continued on next page.)

Primary Examiner—Frederick Krass
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[57] **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

1 Claim, 2 Drawing Sheets

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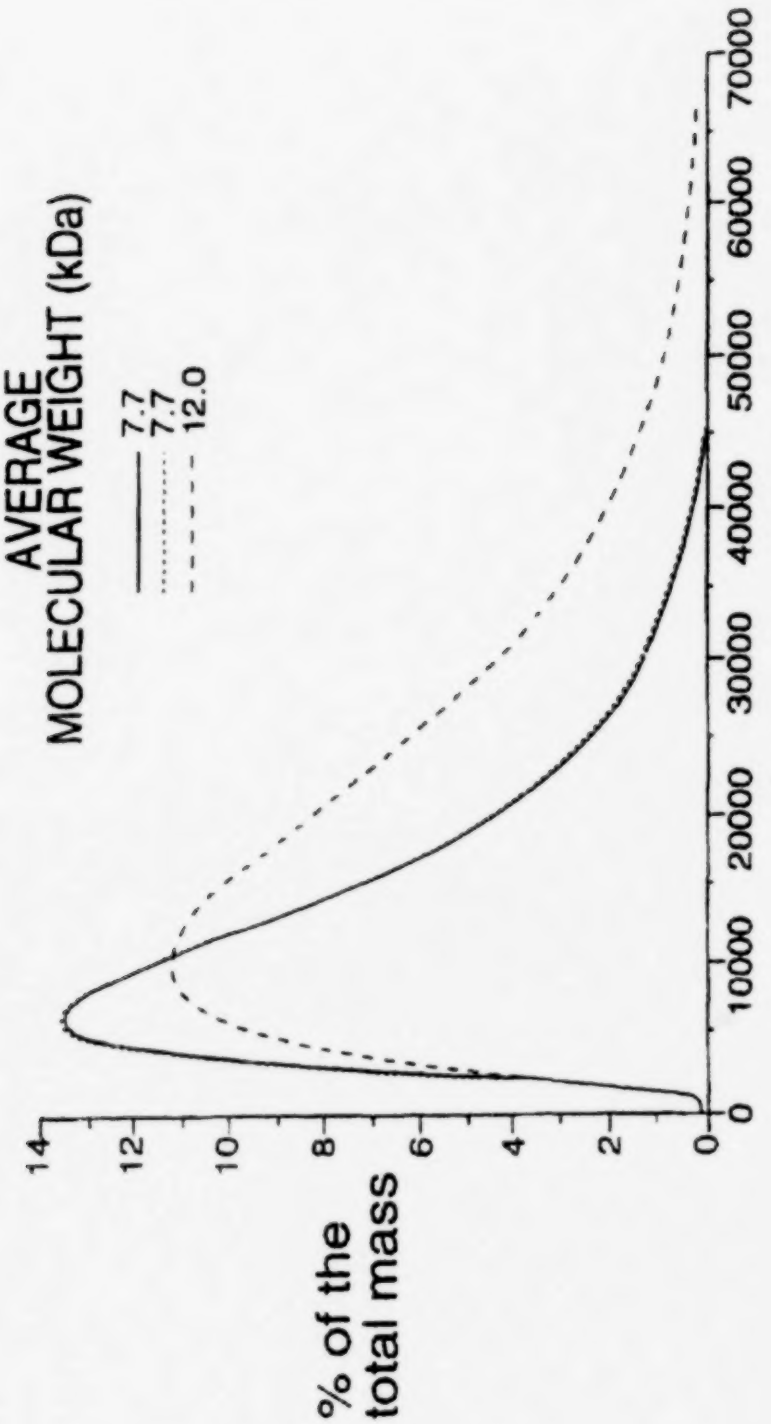
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
% of the
total mass
0
2
4
6
8
10
12
14
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 1

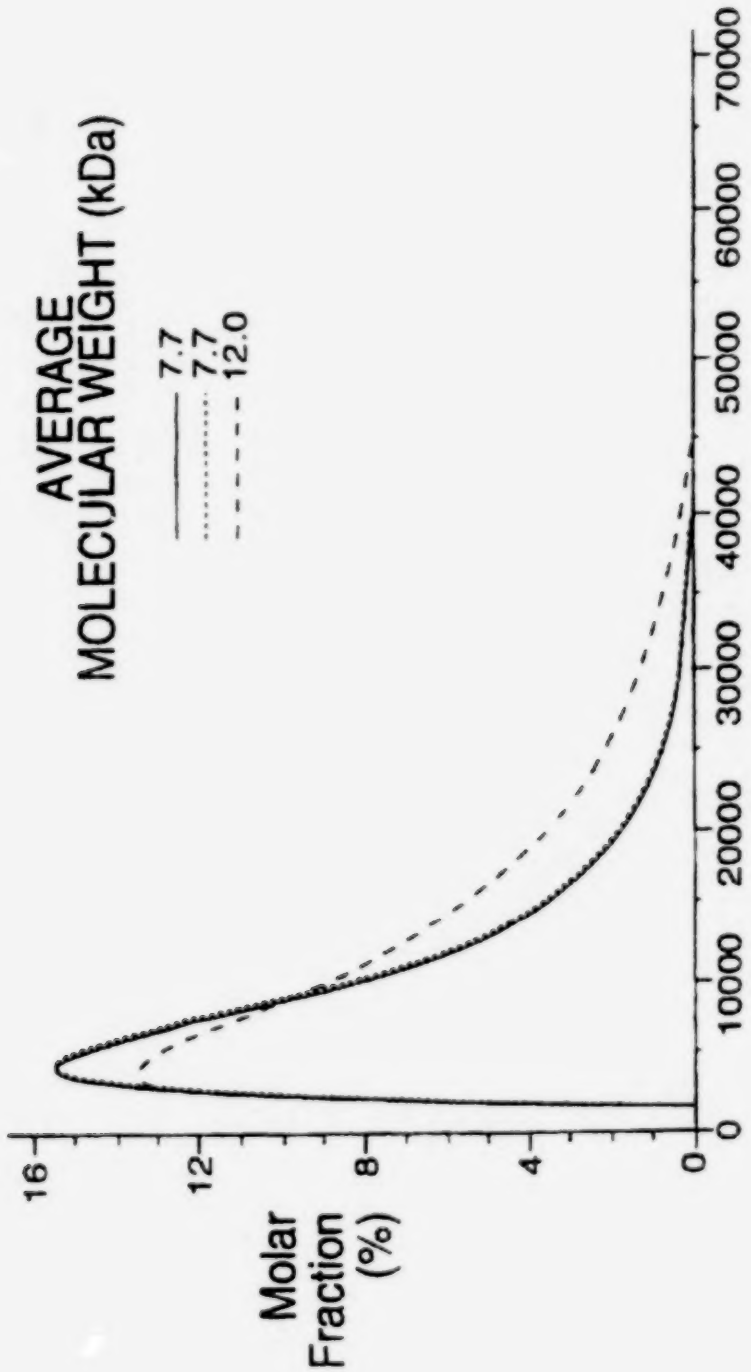
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa. FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and E-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20° to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic method of preparation of low-toxicity copolymer-1 Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600×26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg/ml. in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having

an average molecular weight of 7–8 KDa was isolated between 120–130 minutes (Batch A).

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7–8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A: In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic"

B: In Vitro

RBL—Degranulation test

I. Introduction

Histamine (or serotonin) release from basophile is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-2H$_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (E. L. Basumian, C. Isersky, M. G. Petrino and R. P. Siraganian. Eur. J. Immunol. 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects.

II. Principle of the test method

Rat Basophilic Leukemia cells (RBL-2H$_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250–14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table.

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01–0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6–12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01–0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20°–28° C. a test reaction is performed on every batch at different time periods for example, from 10–50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of low-toxicity copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°-20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5-6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

What is claimed is:

1. A method of manufacturing copolymer-1, comprising reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1, treating said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. **5,800,808**

DATED **September 1, 1998** **Page 1 of 2**

INVENTOR(S) **Konfino, et al**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 1, right column, line 1, change "onExperimen-" to --on Experimen- --

Page 1, right column, line 23, change "Automimmunity" to --Autoimmunity--;

Page 2, left column, line 27, change "1983, pp." to --1983, 42, pp.--;

Page 2, left column, line 14 from bottom, change "1985," to --1985, 35,--;

Page 2, right column, lines 8 and 9, change "The....Sclerosis" to --"The....Sclerosis"--;

Page 2, right column, lines 17 and 18, change "Copolymer 1...(letter)" to --"Coploymer 1... (letter)"--;

Column 1, line 8, change "1994, pp." to --1994, 1, pp.--;

Column 1, line 34, change "Marland" to --Maryland--;

Column 1, lines 35 and 36, delete "Tel-Aviv University, University of Marland School of Medicine,";

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : **5,800,808**

DATED : **September 1, 1998** **Page 2 of 2**

INVENTOR(S) **Konfino, et al**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, line 17, change "γ-benzyl to --γ-benzyl--;
Column 2, line 20, change "γ-benzyl to --γ-benzyl--;
Column 4, line 33, change "γ-benzyl to --γ-benzyl--;
Column 4, line 52, change "γ-benzyl to --γ-benzyl--;
Column 4, line 60, change "omega" to --gamma--;

Signed and Sealed this

Third Day of April, 2001

Attest

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,800,808
APPLICATION NO. : 08/447146
DATED : September 1, 1998
INVENTOR(S) : Konfino et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the face of the patent, # (73) Assignee, change "Veda" to --Yeda--.

Signed and Sealed this

Twenty-second Day of May, 2007

JON W. DUDAS
Director of the United States Patent and Trademark Office

US005981589A

United States Patent [19]

Konfino et al.

[11] Patent Number: 5,981,589

[45] Date of Patent: Nov. 9, 1999

[54] **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

[75] Inventors: **Eliezer Konfino**, Ramat Gan; **Michael Sela**, Rehovot, **Dvora Teitelbaum**, Rehovot; **Ruth Arnon**, Rehovot, all of Israel

[73] Assignee: **Yeda Research and Development Co., Ltd.**, Rehovot, Israel

[21] Appl. No.: **09/032,616**

[22] Filed: **Feb. 27, 1998**

Related U.S. Application Data

[60] Division of application No. 08/447,146, May 22, 1995, Pat. No. 5,800,808, and a continuation in part of application No. 08/344,248, Nov. 23, 1994, abandoned, which is a continuation of application No. 08/248,037, May 24, 1994, abandoned.

[51] **Int. Cl.**[6] **A61K 27/00**

[52] **U.S. Cl.** **514/561**; 424/78.08; 424/78.26; 424/78.29; 525/328; 525/420; 525/434; 525/435

[58] **Field of Search** 514/561; 424/78.08, 424/78.26, 78.29; 525/420, 434, 435, 328

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(List continued on next page.)

Primary Examiner—Frederick Krass
Attorney, Agent, or Firm—Kenyon & Kenyon

[57] **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

1 Claim, 2 Drawing Sheets

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Clinical Trial Protocol No. 9002; first patient enrolled Jun. 17, 1993.

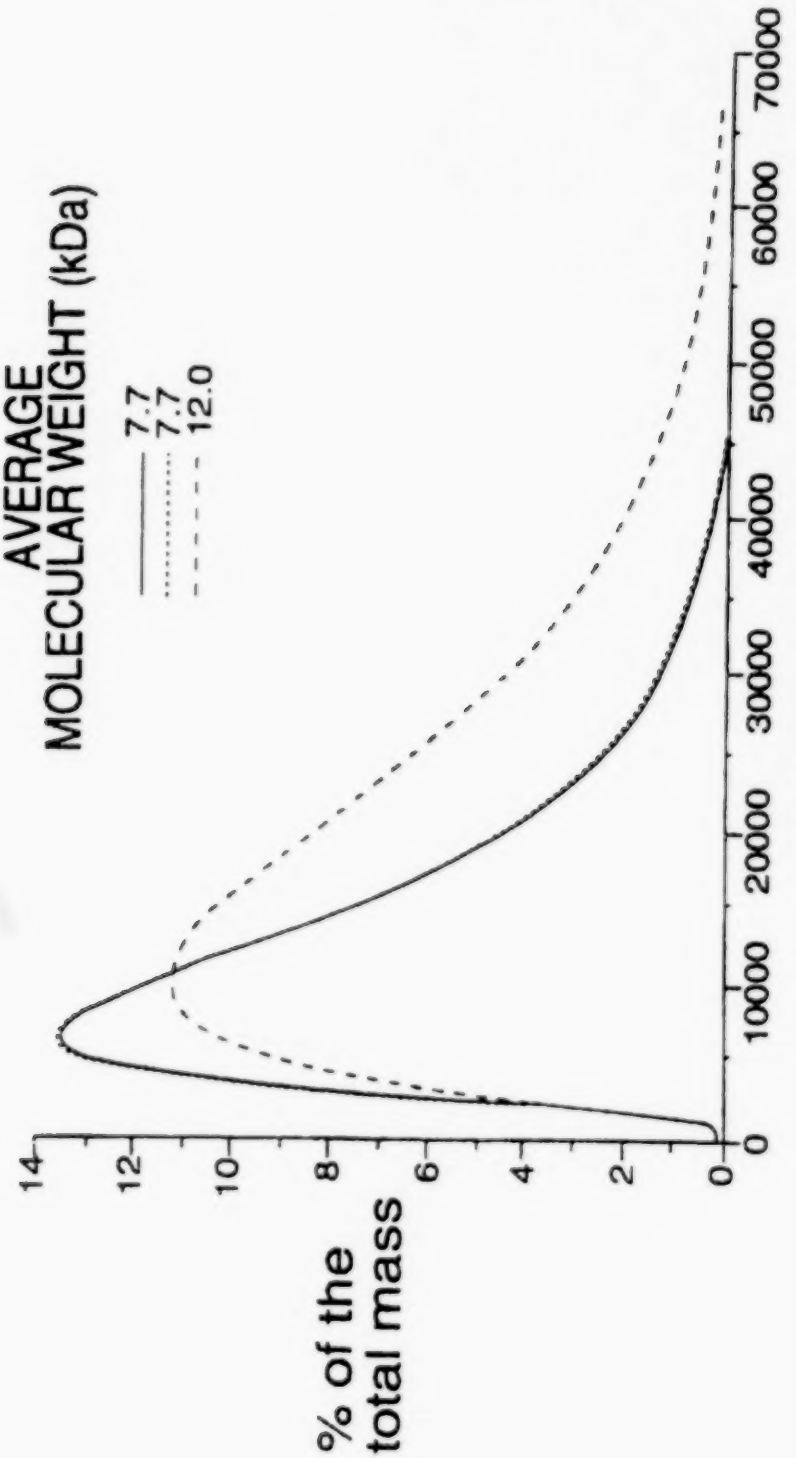
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
% of the
total mass
0
2
4
6
8
10
12
14
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 1

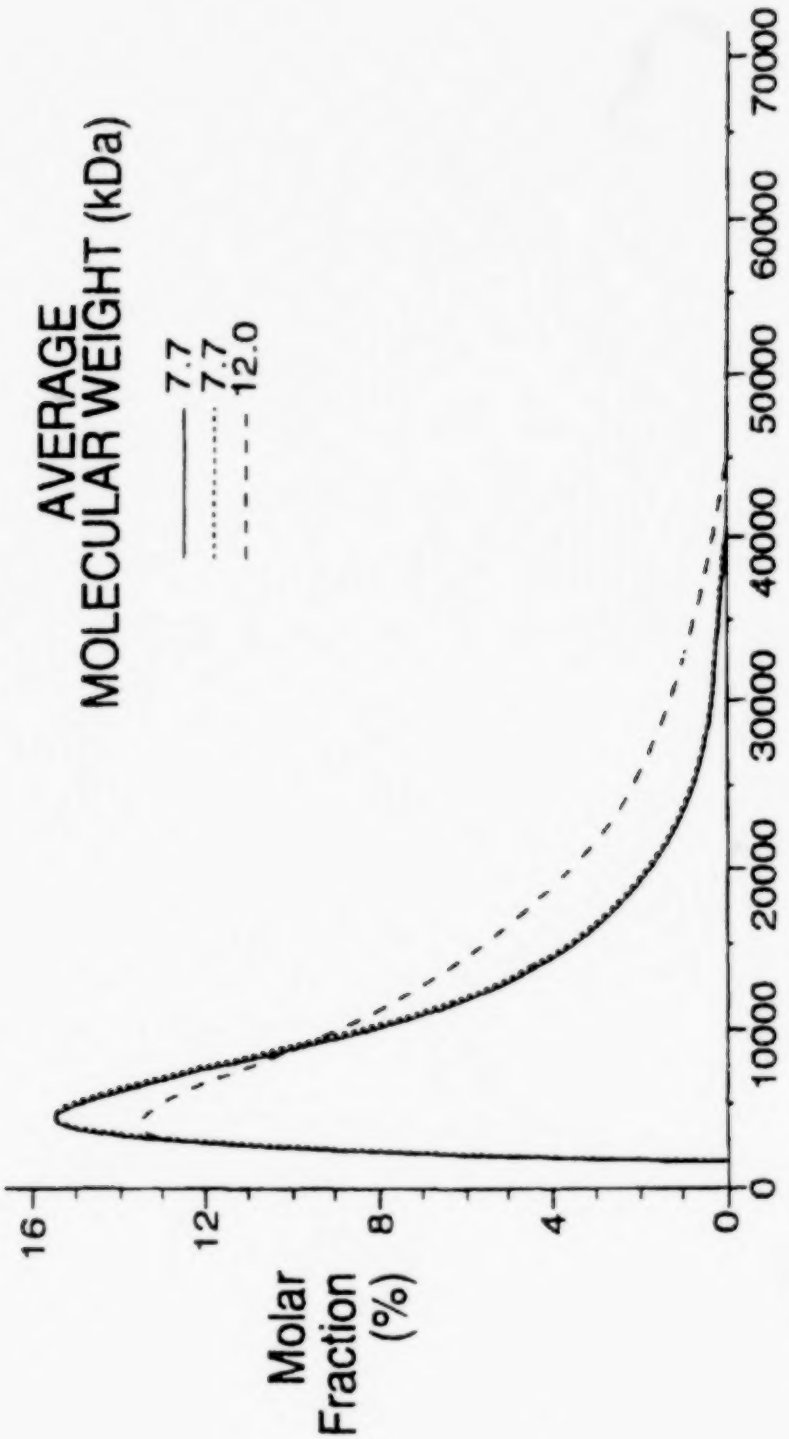
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a divisional of U.S. Ser. No. 08/447,146, filed May 22, 1995, which is now U.S. Pat. No. 5,800,808 and is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242, and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2.5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa. FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa. Copolymer1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and L-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic Method of Preparation of Low-toxicity Copolymer-1

Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600x26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg/ml, in 0.2M ammonium acetate pH 5.0) were loaded on the column and

fractions were collected every 10 minutes. A fraction having an average molecular weight of 7-8 KDa was isolated between 120-130 minutes (Batch A)

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A. In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B. In Vitro

RBL—Degranulation Test

I. Introduction

Histamine (or serotonin) release from basophils is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-$2H_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (L. L. Basumian, C. Isersky, M. G. Petrino and R. P. Siraganian. Lur. J. Immunol 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and or systemic side effects.

II. Principle of the Test Method

Rat Basophilic Leukemia cells (RBL-$2H_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250-14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table.

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	≥5	66.9
14,500	≥5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Icitelbaum et al. Lur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Icitelbaum et al. Lur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20-28° C. a test reaction is performed on every batch at different time periods for example, from 10-50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of Low-toxicity Copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°–20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5–6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

We claim:

1. Copolymer-1 having a molecular weight of about 5 to 9 kilodaltons, made by a process comprising the steps of:

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1,

treating said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and

purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,981,589
DATED : November 9, 1999
INVENTOR(S) : Eliezer Kanfino et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below

Title page,

Item [60], change "division of application No. 08/447,146, May 22, 1995, Pat. No. 5,800,808, and a continuation-in-part" to -- division of application No. 08/477,146, May 22, 1995, Pat. No. 5,800,808, which is a continuation-in part --

Signed and Sealed this

Twenty-third Day of December, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006048898A

United States Patent [19]

Konfino et al.

[11] Patent Number: 6,048,898

[45] Date of Patent: *Apr. 11, 2000

[54] **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

[75] Inventors: **Eliezer Konfino**, Ramat Gan; **Michael Sela**, Rehovot; **Dvora Teitelbaum**, Rehovot; **Ruth Arnon**, Rehovot, all of Israel

[73] Assignee: **Yeda Research and Development Co., Ltd.**, Rehovot, Israel

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/032,334**

[22] Filed: **Feb. 27, 1998**

Related U.S. Application Data

[63] Continuation of application No. 08/447,149, May 22, 1995, Pat. No. 5,800,808, which is a continuation-in-part of application No. 08/344,248, Nov. 23, 1994, abandoned, which is a continuation of application No. 08/248,037, May 24, 1994, abandoned.

[51] **Int. Cl.**[7] **A01N 43/16**; A61K 31/35; C08L 283/04; C08G 69/48; C08L 77/00

[52] **U.S. Cl.** **514/561**; 424/78.08; 424/78.26; 424/78.29; 525/420; 525/434; 525/435; 528/328

[58] **Field of Search** 514/561; 424/78.08, 424/78.26, 78.29; 525/420, 434, 435; 528/328

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Primary Examiner—Frederick Krass
Attorney, Agent, or Firm—Kenyon & Kenyon

[57] **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

6 Claims, 2 Drawing Sheets

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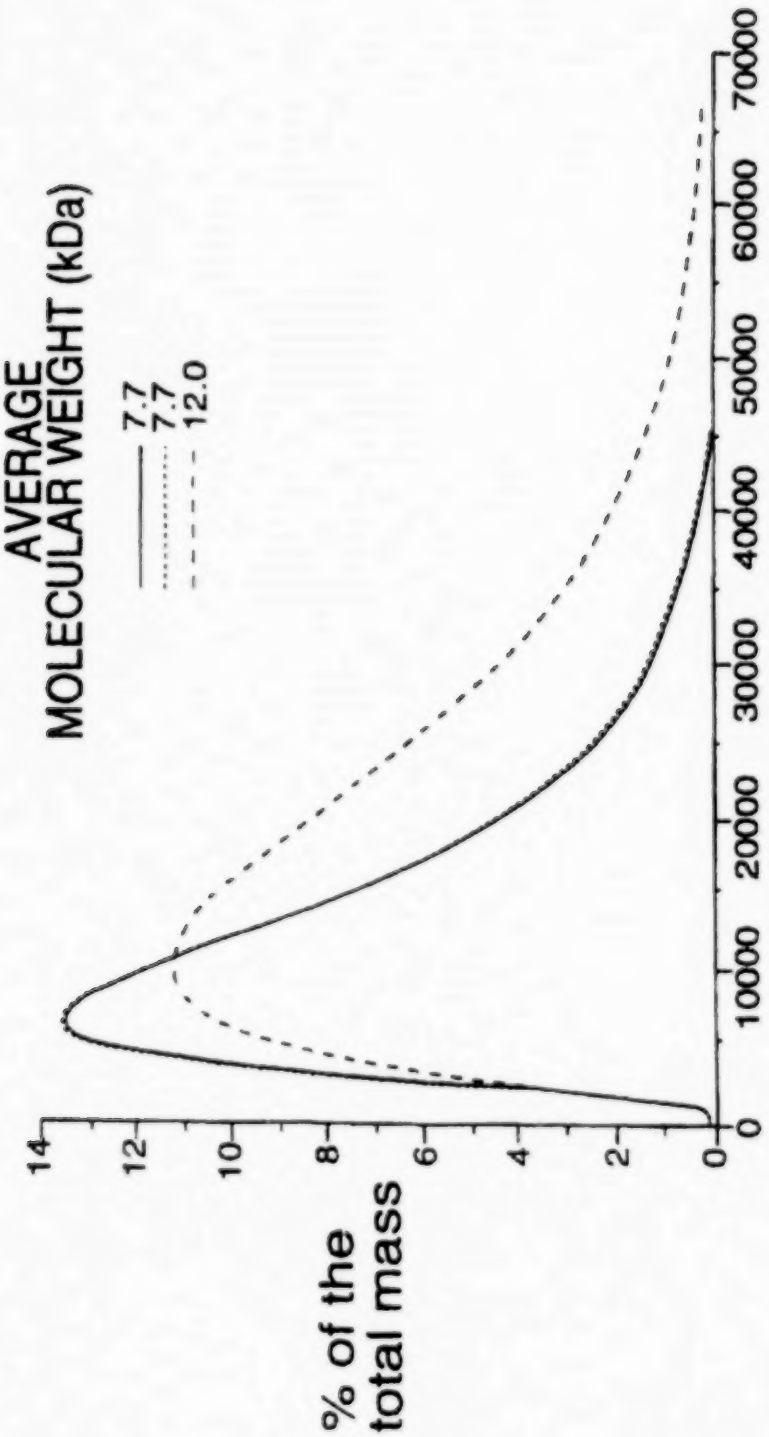
AVERAGE MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
% of the total mass
0
2
4
6
8
10
12
14
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 1

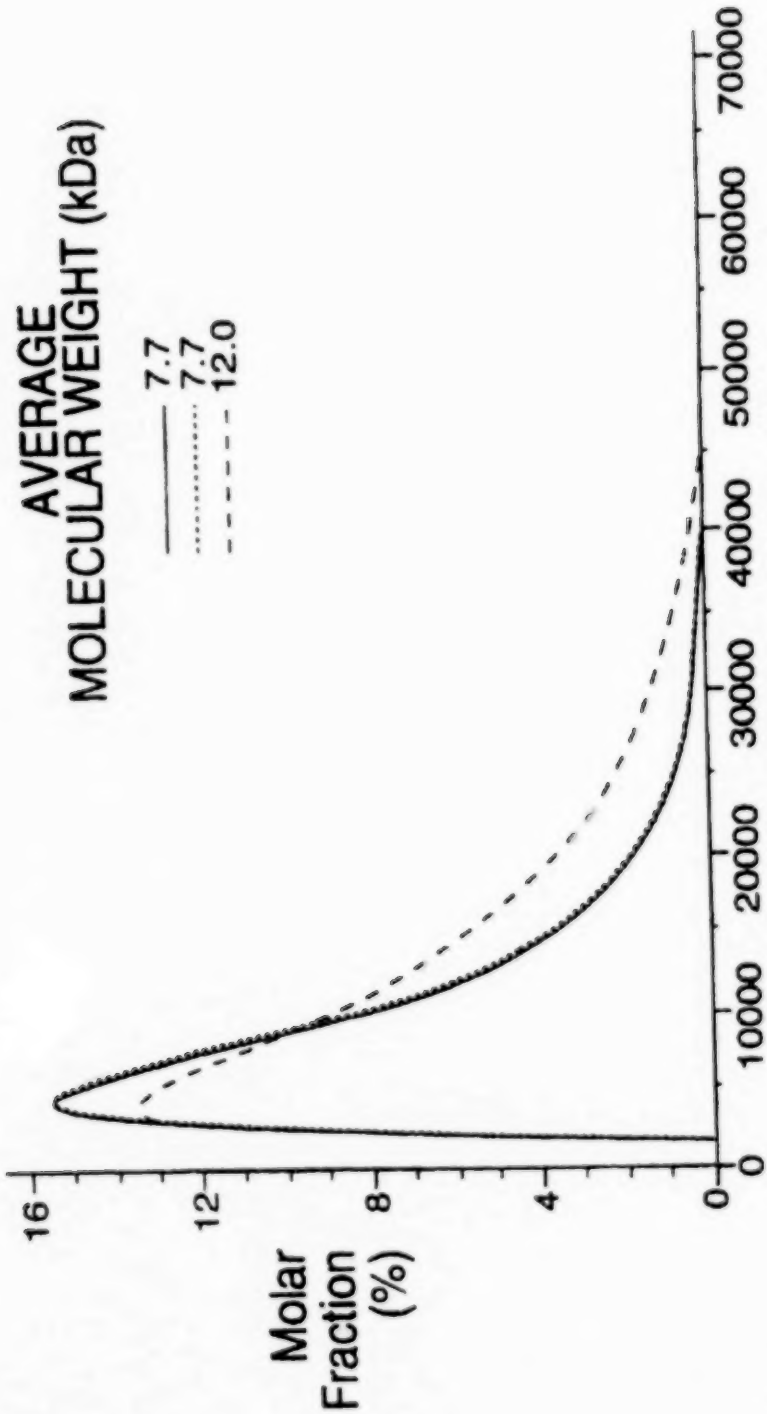
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a continuation of U.S. Ser. No. 08/447,146, filed May 22, 1995, now U.S. Pat. No. 5,800,808, which is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Lur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAL). EAL is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAL (Lur. J. Immunol. [1971] 1:242, U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6.2:5.1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa.

FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and L-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic method of preparation of low-toxicity copolymer-1

Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600x26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetonic solution

was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg/ml, in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an average molecular weight of 7-8 KDa was isolated between 120-130 minutes (Batch A)

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A: In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B: In Vitro

RBL—Degranulation test

I. Introduction

Histamine (or serotonin) release from basophils is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-$2H_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (L. I. Basunian, C. Isersky, M. G. Petrino and R. P. Siraganian. Eur. J. Immunol. 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and or systemic side effects.

II. Principle of the test method

Rat Basophilic Leukemia cells (RBL-$2H_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250-14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table.

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,400	≥5	66.9
14,500	≥5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), L-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01–0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20–28° C. a test reaction is performed on every batch at different time periods for example, from 10–50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of low-toxicity copolymer-1

20g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 10 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°–20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5–6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

What is claimed is:

1. A method of manufacturing copolymer-1 of a predetermined molecular weight profile, comprising the steps of

selecting a predetermined molecular weight profile,

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having the predetermined molecular weight profile, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and

treating said trifluoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile.

2. The method of claim 1, wherein said protected copolymer-1 reacted with hydrobromic acid for about 10–50 hours at a temperature of about 20–28° C.

3. The method of claim 2, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26° C.

4. A method of manufacturing trifluoroacetyl copolymer-1 having a predetermined molecular weight profile, comprising the steps of:

selecting a predetermined molecular weight profile, and then

reacting protected copolymer-1 with hydrobromic acid for a time and at a temperature predetermined by test reaction to provide trifluoroacetly copolymer-1 having the predetermined molecular weight profile.

5. The method of claim 4, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 10–50 hours at a temperature of about 20–28° C.

6. The method of claim 5, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26° C.

* * * * *

US006054430A

United States Patent [19]

Konfino et al.

[11] Patent Number: 6,054,430

[45] Date of Patent: Apr. 25, 2000

[54] **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

[75] Inventors: **Eliezer Konfino**, Ramat Gan; **Michael Sela**, Rehovot; **Dvora Teitelbaum**, Rehovot; **Ruth Arnon**, Rehovot, all of Israel

[73] Assignee: **Yeda Research and Development Co., Ltd.**, Rehovot, Israel

[21] Appl. No.: **09/032,647**

[22] Filed: **Feb. 27, 1998**

Related U.S. Application Data

[60] Division of application No. 08/447,146, May 22, 1995, Pat. No. 5,800,808, which is a continuation-in-part of application No. 08/344,248, Nov. 23, 1994, abandoned, which is a continuation of application No. 08/248,037, May 24, 1994, abandoned.

[51] **Int. Cl.**[7] **A61K 31/785**; A61K 38/16

[52] **U.S. Cl.** **514/12**; 424/78.17; 514/903; 525/420

[58] **Field of Search** 514/903, 12; 424/78.26

[56] **References Cited**

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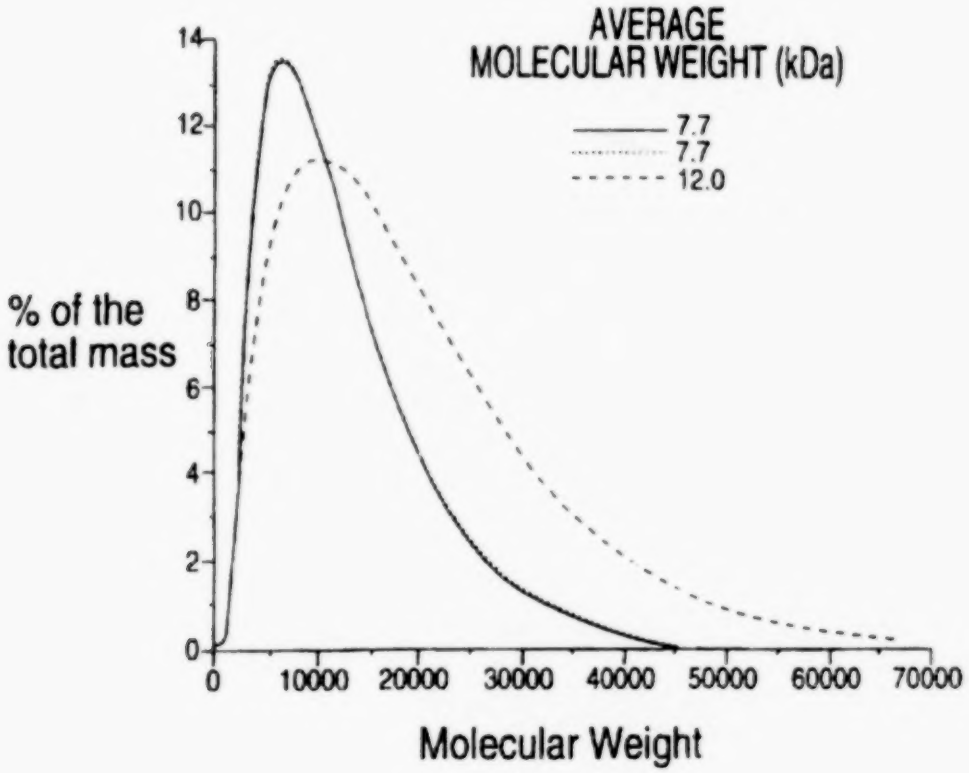
Primary Examiner—Peter F. Kulkosky

Attorney, Agent, or Firm—Kenyon & Kenyon

[57] **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

6 Claims, 2 Drawing Sheets



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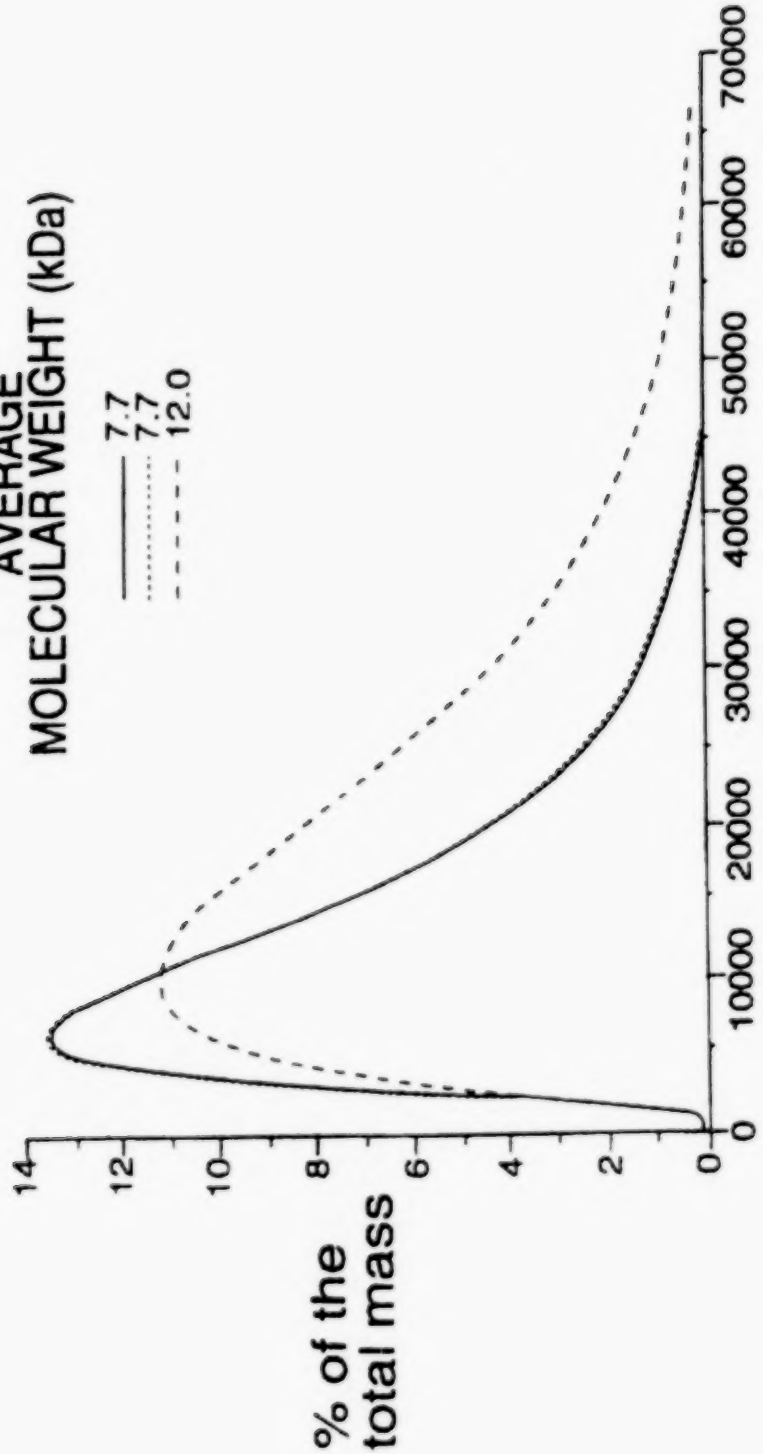

FIG. 1

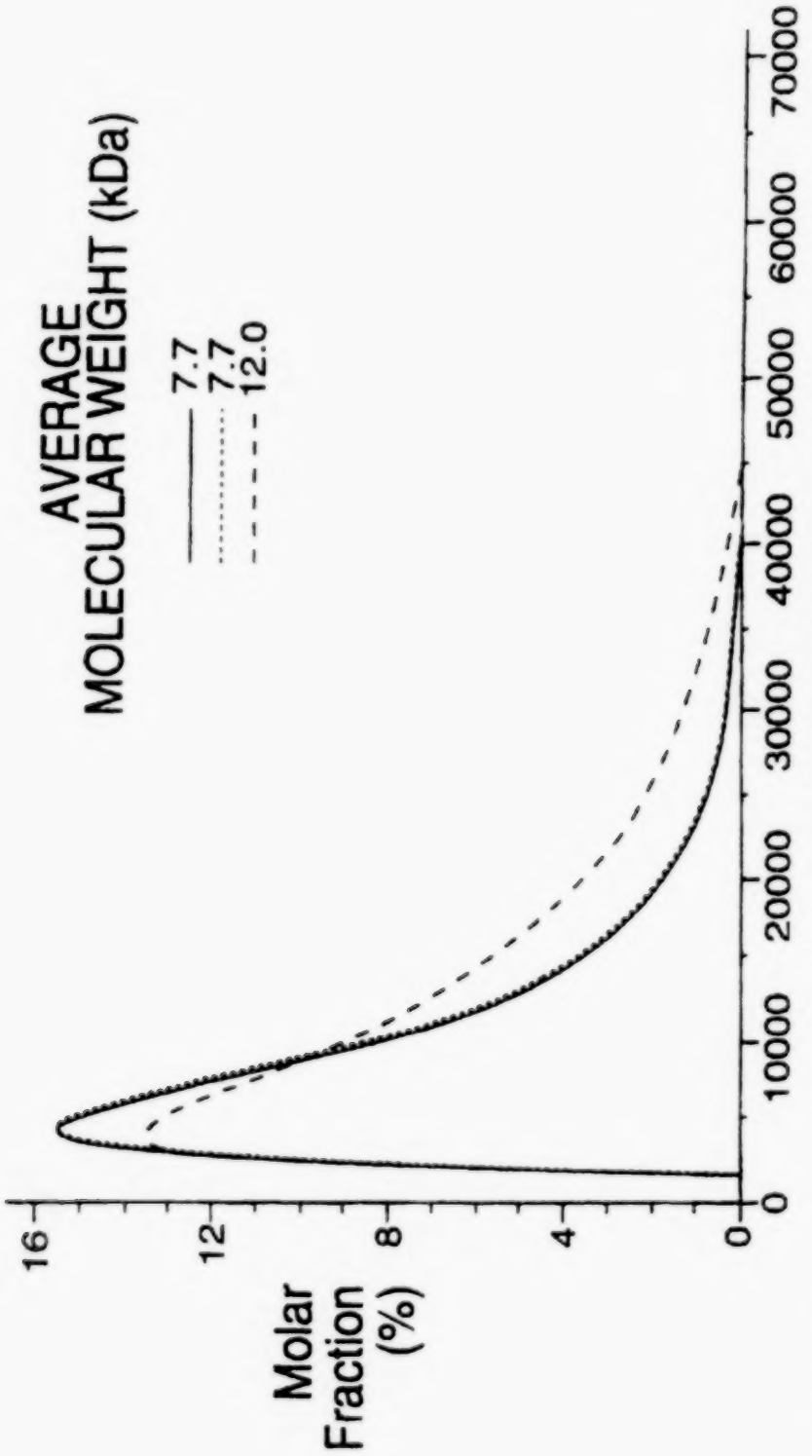
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a divisional of U.S. Ser. No. 08/447,146, filed on May 22, 1995, now U.S. Pat. No. 5,800,808 which is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, abandoned which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994 abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2.5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa.

FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and L-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic Method of Preparation of Low-Toxicity Copolymer-1

Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600×26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg of, in 0.2M ammo-

nium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an average molecular weight of 7-8 KDa was isolated between 120-130 minutes (Batch A).

Molecular Weight Analyses

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the total had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A. In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B. In Vitro

RBL—Degranulation Test

I. Introduction

Histamine (or serotonin) release from basophils is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-$2H_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (L. I. Basunian, C. Isersky, M. G. Petrino and R. P. Siraganian. Eur. J. Immunol. 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects.

II. Principle of the Test Method

Rat Basophilic Leukemia cells (RBL-$2H_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250-14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table:

Average M.W. (KDa)	% of species with M.W. over 40 KDa	% Serotonin Release
6.25	<2.5	12.4
7.3	<2.5	[illegible]
13	>5	[illegible]
14.5	>5	[illegible]

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamic residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20-26° C.

a test reaction is performed on every batch at different time periods for example, from 10–50 hours. The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of Low-Toxicity Copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°–20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5–6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

We claim:

1. Copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa, prepared by a process comprising the steps of:

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and

treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2kDa to about 20kDa.

2. The copolymer-1 of claim 1 wherein said protected copolymer-1 is reacted with hydrobromic acid for about 10–50 hours at a temperature of about 20–28° C.

3. The copolymer-1 of claim 1, wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26° C.

4. Trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa, produced by a process comprising the steps of reacting protected copolymer-1 with hydrobromic acid for a time and at a temperature predetermined by test reaction.

5. The trifluoroacetyl copolymer-1 of claim 4 wherein said protected copolymer-1 is reacted with hydrobromic acid for about 10–50 hours at a temperature of about 20–28° C.

6. The trifluoroacetyl copolymer-1 of claim 5 wherein said protected copolymer-1 is reacted with hydrobromic acid for about 17 hours at a temperature of about 26° C.

* * * * *

US006342476B1

(12) **United States Patent**
Konfino et al.

(10) **Patent No.: US 6,342,476 B1**
(45) **Date of Patent: Jan. 29, 2002**

(54) **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

(75) Inventors: **Eliezer Konfino**, Ramat Gan; **Michael Sela**, Rehovot; **Dvora Teitelbaum**, Rehovot; **Ruth Arnon**, Rehovot, all of (IL)

(73) Assignee: **Yeda Research & Development Company Limited**, Rehovot (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/510,141**

(22) Filed: **Feb. 22, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/032,334, filed on Feb. 27, 1998, now Pat. No. 6,048,898, which is a continuation of application No. 08/447,146, filed on May 22, 1995, now Pat. No. 5,800,808, which is a continuation in part of application No. 08/344,248, filed on Nov. 23, 1994, now abandoned, which is a continuation of application No. 08/248,037, filed on May 24, 1994, now abandoned.

(51) **Int. Cl.**[7] **A01N 43/16**; A61K 31/35

(52) **U.S. Cl.** **514/2**; 514/12; 514/903; 424/78.37

(58) **Field of Search** 514/2, 12, 903; 424/78.37

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(57) **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

1 Claim, 2 Drawing Sheets

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U.S. Patent Jun. 29, 2002 Sheet 1 of 2 US 6,342,476 B1

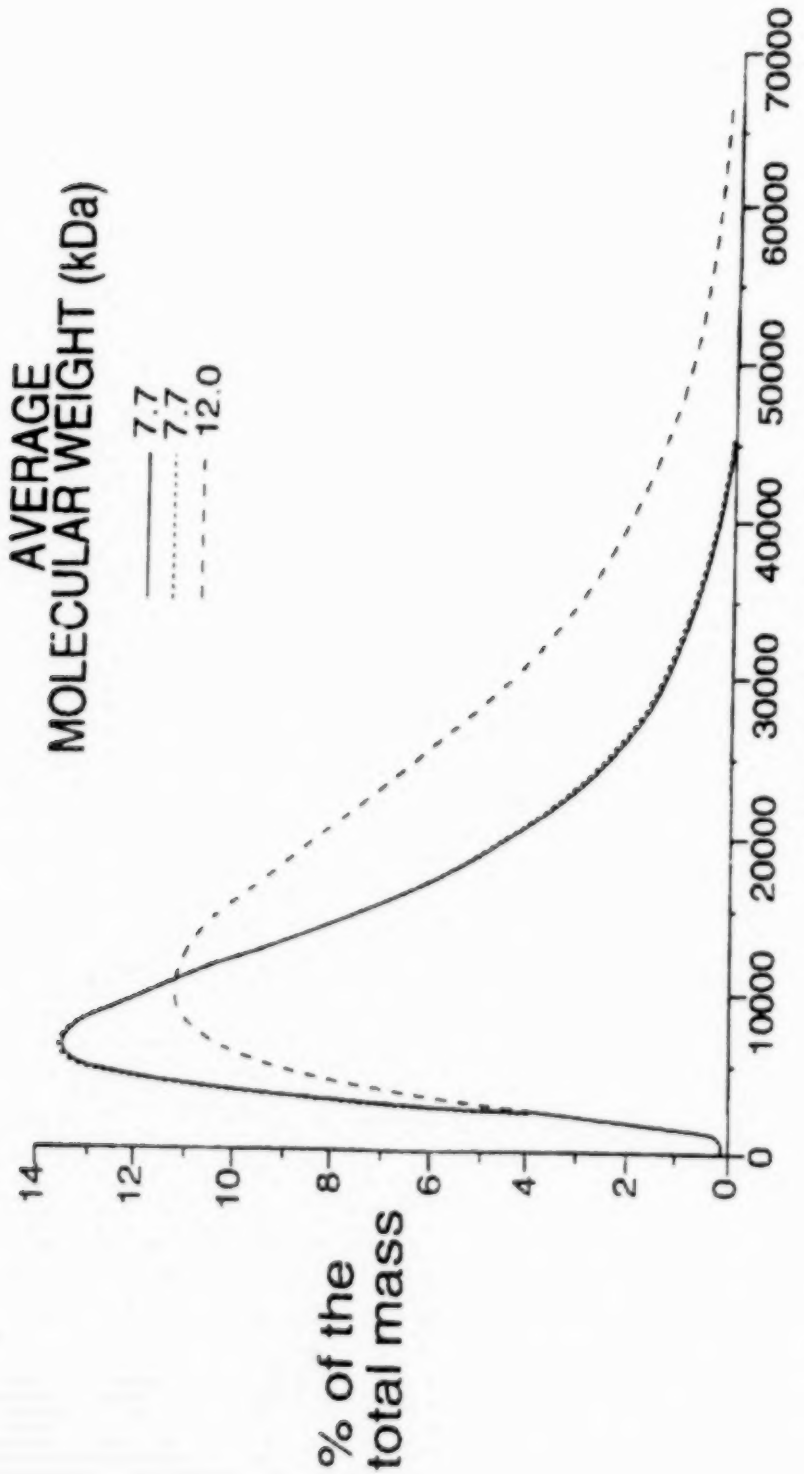

FIG. 1

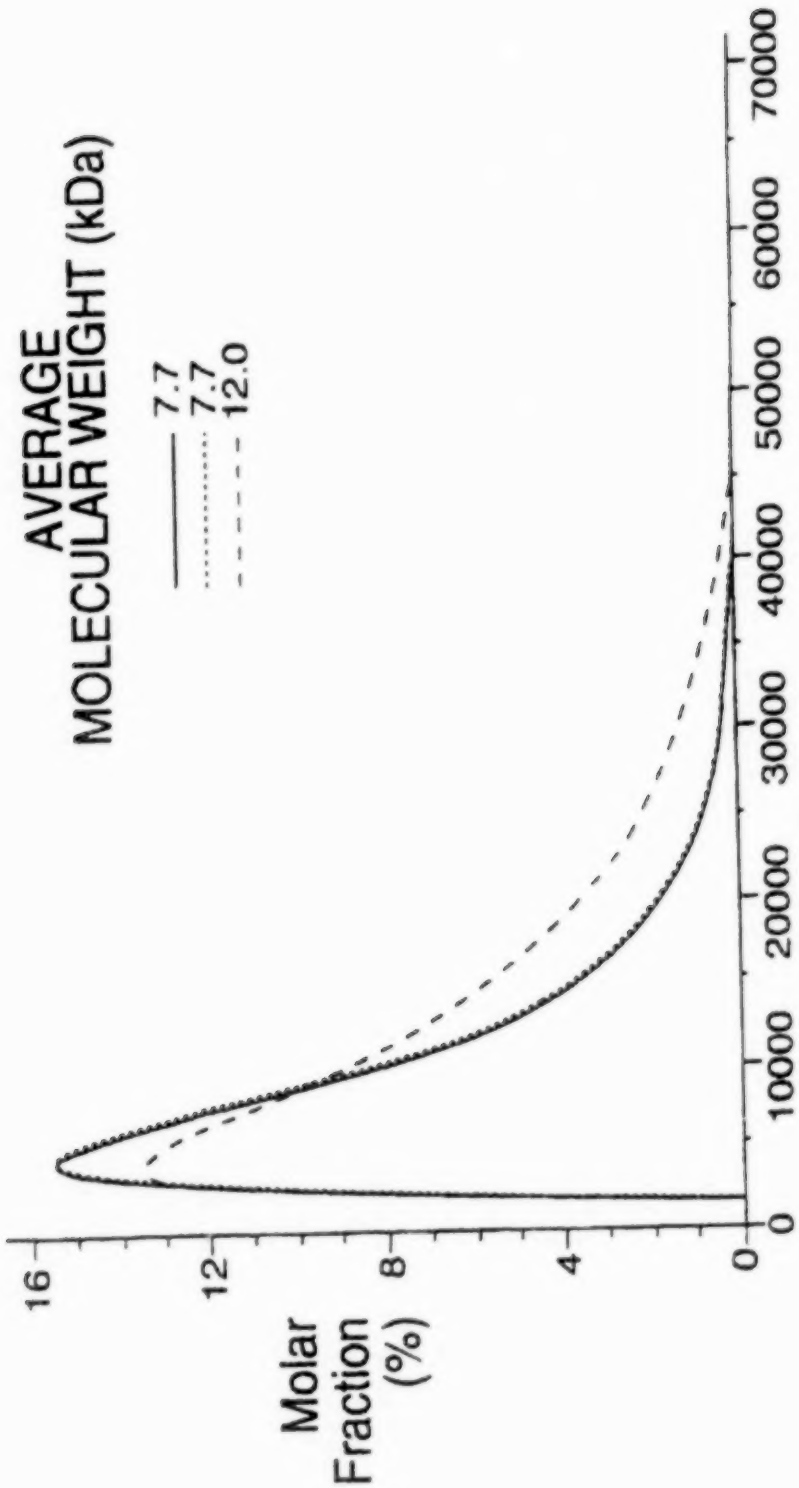
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a continuation of application Ser. No. 09/032,334, filed Feb. 27, 1998, U.S. Pat. No. 6,048,898, which is a continuation of U.S. Ser. No. 08/447,146, filed May 22, 1995, now U.S. Pat. No. 5,800,808, which is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa. FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and ε-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic Method of Preparation of Low-Toxicity Copolymer-1

Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600x26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution

was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg/ml, in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an average molecular weight of 7-8 KDa was isolated between 120-130 minutes (Batch A).

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A: In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B: In Vitro

RBL —Degranulation test

I. Introduction

Histamine (or serotonin) release from basophils is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-$2H_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (L. L. Bausman, C. Isersky, M. G. Petrino and R. P. Siraganian Eur. J. Immunol 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects.

II. Principle of the test method

Rat Basophilic Leukemia cells (RBL-$2H_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250-14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table:

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,600	<2.5	21.0
13,500	>5	66.0
14,500	>5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamic residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20–28° C. a test reaction is performed on every batch at different time periods for example, from 10–50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetylcopolymer-1.

Preparation of Low-toxicity Copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°-20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5–6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

What is claimed is:

1. A method for treating multiple sclerosis, comprising administering to a subject in need thereof, a pharmaceutically effective amount of a copolymer-1 fraction wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons, and wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons, wherein said copolymer-1 fraction is prepared by a process comprising the steps of:

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and

treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa.

* * * * *

US006362161B1

(12) **United States Patent**
Konfino et al.

(10) **Patent No.: US 6,362,161 B1**
(45) **Date of Patent: *Mar. 26, 2002**

(54) **COPOLYMER-1 IMPROVEMENTS ON COMPOSITIONS OF COPOLYMERS**

(75) Inventors: **Eliezer Konfino**, Ramat Gan; **Michael Sela**, Rehovot; **Dvora Teitelbaum**, Rehovot; **Ruth Arnon**, Rehovot, all of (IL)

(73) Assignee: **Yeda Research & Development Company Limited**, Rehovot (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer

(21) Appl. No.: **09/510,466**

(22) Filed: **Feb. 22, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/032,647, filed on Feb. 27, 1998, now Pat. No. 6,054,430, which is a continuation of application No. 08/447,146, filed on May 22, 1995, now Pat. No. 5,800,808, which is a continuation-in-part of application No. 08/344,248, filed on Nov. 23, 1994, now abandoned, which is a continuation of application No. 08/248,147, filed on May 24, 1994, now abandoned.

(51) **Int. Cl.**[7] **A61K 27/00**

(52) **U.S. Cl.** **514/2**; 514/12; 514/803; 424/78.37

(58) **Field of Search** 514/2, 12, 803; 424/78.37

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(57) **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

1 Claim, 2 Drawing Sheets

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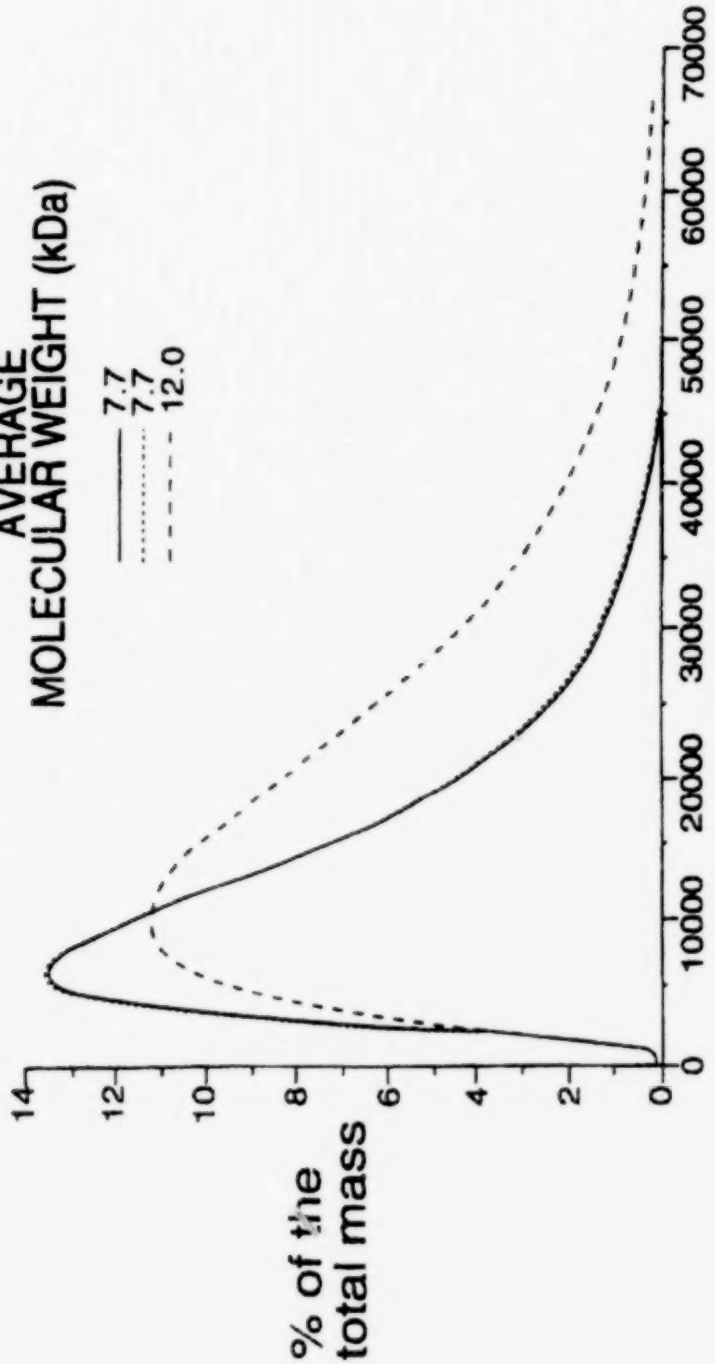
AVERAGE MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
% of the total mass
0
2
4
6
8
10
12
14
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 1

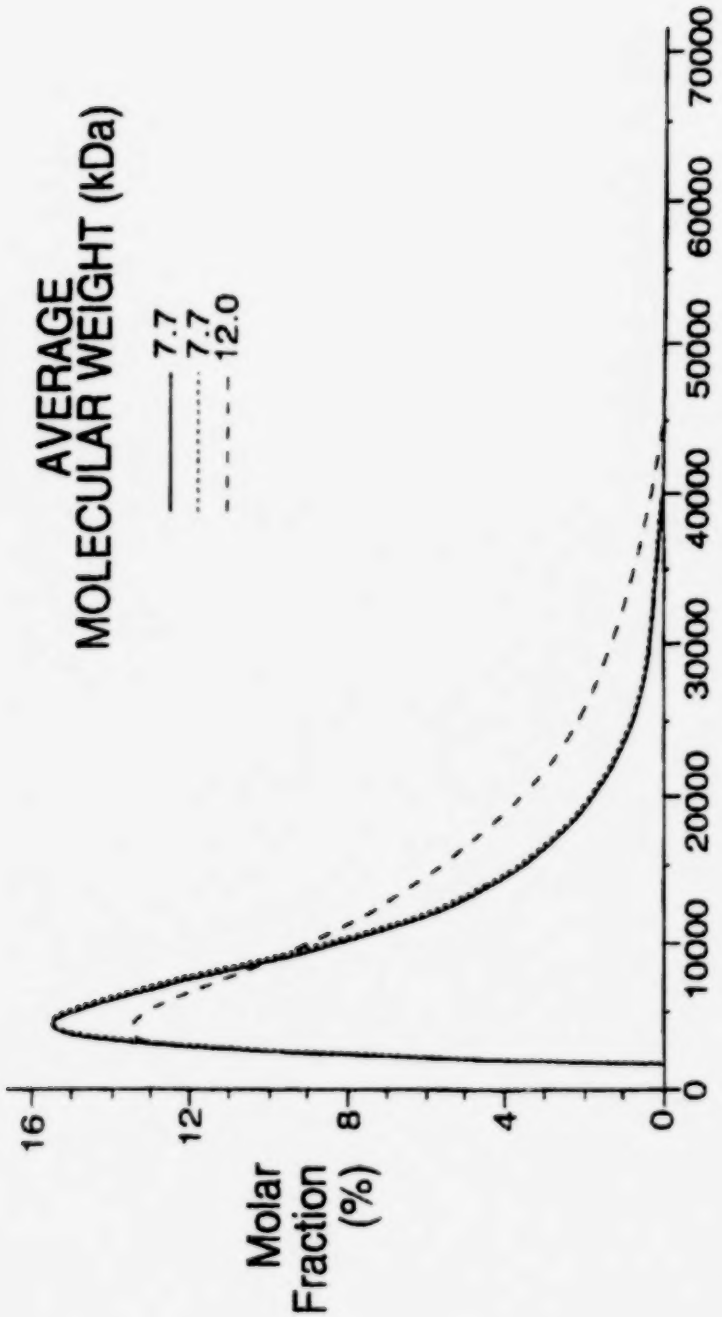
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS ON COMPOSITIONS OF COPOLYMERS

This application is a continuation of application Ser. No. 09/032,647 filed Feb. 27, 1998, now U.S. Pat. No. 6,054,430, which is a continuation of U.S. Ser. No. 08/447,146, filed May 22, 1995, now U.S. Pat. No. 5,800,808, which is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242, and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2.5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa.

FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and L-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic Method of Preparation of Low-toxicity Copolymer-1

Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600×26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2 M ammonium acetate buffer pH

5.0. 30 ml copolymer-1 samples (20 mg/ml, in 0.2 M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an average molecular weight of 7-8 KDa was isolated between 120-130 minutes (Batch A).

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A. In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B. In Vitro

RBL—Degranulation Test

I. Introduction

Histamine (or serotonin) release from basophils is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-$2H_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (L. I. Basuman, C. Isersky, M. G. Petrino and R. P. Siraganian. Eur. J. Immunol. 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and or systemic side effects.

II. Principle of the Test Method

Rat Basophilic Leukemia cells (RBL-$2H_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 ng of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250-14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table.

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,800	<2.5	21.0
13,000	>5	69.0
14,500	>5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g) γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da

depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20–28° C. a test reaction is performed on every batch at different time periods for example, from 10–50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of Less-toxicity Copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°–20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5–6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

What is claimed is:

1. A composition for the treatment of multiple sclerosis comprising a pharmaceutically effective amount of a copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons; and wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons, wherein said copolymer-1 fraction is prepared by a process comprising the steps of:

reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa, wherein said reaction takes place for a time and at a temperature predetermined by test reaction, and

treating said trifluoroacetyl copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa with aqueous piperidine solution to form copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 kDa to about 20 kDa.

* * * * *

US006620847B2

(12) **United States Patent**
Konfino et al.

(10) **Patent No.: US 6,620,847 B2**
(45) **Date of Patent: Sep. 16, 2003**

(54) **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/014,477**

(22) Filed: **Dec. 14, 2001**

(65) **Prior Publication Data**

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(63) Continuation of application No. 09/510,446, filed on Feb. 22, 2000, now Pat. No. 6,362,161, which is a continuation of application No. 09/032,334, filed on Feb. 27, 1998, now Pat. No. 6,048,898, which is a continuation of application No. 08/447,146, filed on May 22, 1995, now Pat. No. 5,800,808, which is a continuation-in-part of application No. 08/344,248, filed on Nov. 23, 1994, now abandoned, which is a continuation of application No. 08/248,037, filed on May 24, 1994, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/195**

(52) **U.S. Cl.** **514/561**; 424/78.08; 424/78.26; 424/78.29; 525/420; 525/434; 525/435; 528/328

(58) **Field of Search** 514/561; 424/78.08, 424/78.26, 78.29; 525/420, 434, 435; 528/328

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(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

9 Claims, 2 Drawing Sheets

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U.S. Patent Sep. 16, 2003 Sheet 1 of 2 US 6,620,847 B2

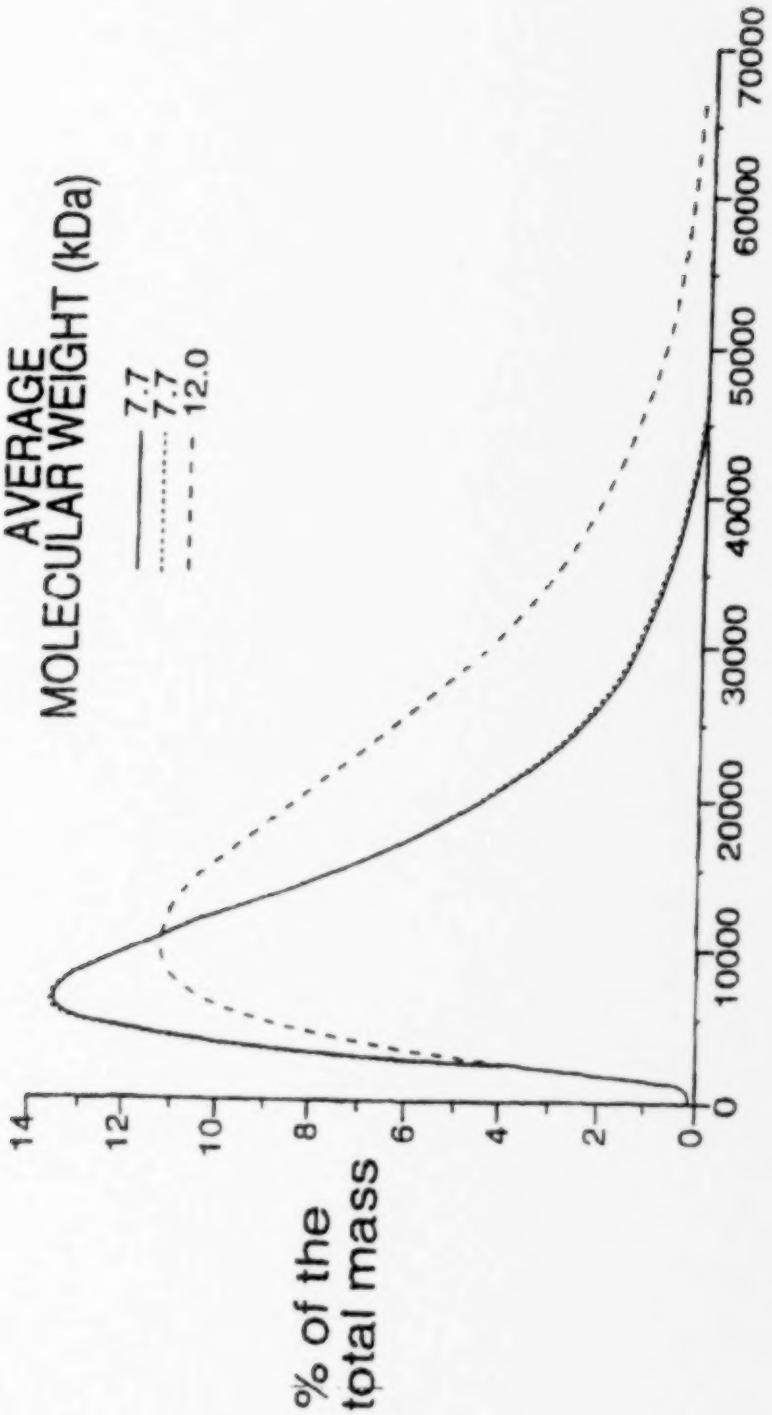


FIG. 1

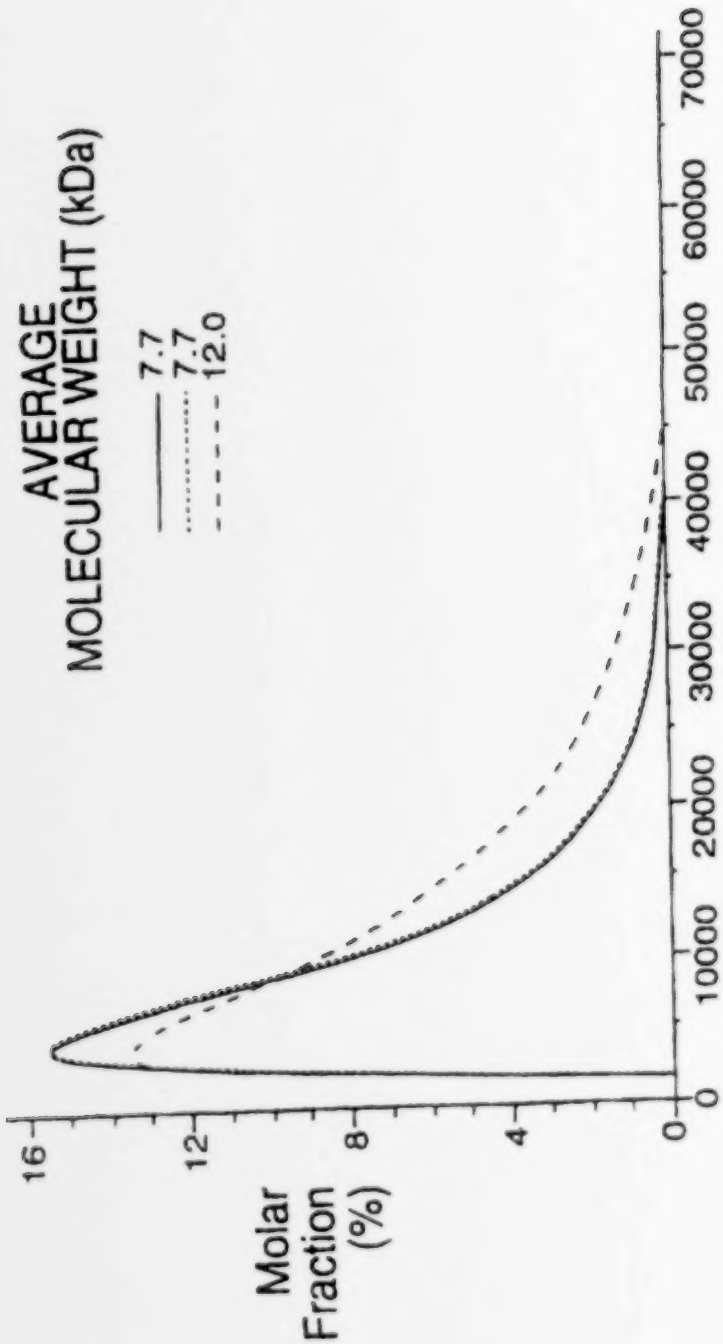

AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a continuation of application Ser. No. 09/510,466, filed Feb. 22, 2000, now U.S. Pat. No. 6,362,161, which is a continuation of U.S. Ser. No. 09/032,334 filed Feb. 27, 1998, now U.S. Pat. No. 6,048,898, which is a continuation of U.S. Ser. No. 08/447,146, filed May 22, 1995, now U.S. Pat. No. 5,800,808, which is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Lur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa. FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and L-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic method of preparation of low-toxicity copolymer-1. Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600x26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH

5.0. 30 ml copolymer-1 samples (20 mg/ml, in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an average molecular weight of 7-8 KDa was isolated between 120-130 minutes (Batch A)

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12)

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A: In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B: In Vitro

RBL-Degranulation Test

I. Introduction

Histamine (or serotonin) release from basophils is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-2H$_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (L. J. Basumian, C. Isersky, M. G. Petrino and R. P. Siraganian. Lur. J. Immunol 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and or systemic side effects.

II. Principle of the Test Method

Rat Basophilic Leukemia cells (RBL-2H$_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250–14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table:

Average M.W. (Daltons)	% of Species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.1
13,950	>5	66.9
14,500	>5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Lur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01–0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6–12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Lur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01–0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da

depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20–28° C. a test reaction is performed on every batch at different time periods for example, from 10–50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of Low-Toxicity Copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°–20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5–6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

What is claimed is:

1. Copolymer-1 having a molecular weight of about 4 to about 9 kilodaltons, made by a process comprising:

treating trifluoroacetyl copolymer-1 with aqueous piperidine to form a solution of copolymer-1; and

purifying copolymer-1, thereby producing copolymer-1 having a molecular weight of about 4 to about 9 kilodaltons.

2. Copolymer-1 made by the process of claim 1, wherein the process further comprises reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1.

3. Copolymer-1 made by the process of claim 2, wherein the hydrobromic acid comprises about 33% hydrogen bromide in acetic acid.

4. Copolymer-1 made by the process of claim 2, wherein the process further comprises polymerizing N-carboxyanhydride derivatives to form protected copolymer-1.

5. Copolymer-1 made by the process of claim 4, wherein the polymerizing step comprises providing a diethylamine initiator.

6. Copolymer-1 made by the process of claim 1, wherein the process further comprises adding acetic acid subsequent to the treating step.

7. Copolymer-1 made by the process of claim 1, wherein the purifying step comprises filtration.

8. A method of manufacturing trifluoroacetyl copolymer-1 having a predetermined molecular weight profile, comprising the steps of:

selecting a predetermined molecular weight profile, and then

reacting protected copolymer-1 with hydrobromic acid at about 26° C. for a time predetermined by test reaction to provide trifluoroacetyl copolymer-1 having the predetermined molecular weight profile.

9. The method of claim 7, further comprising a step of treating the trifluoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,620,847 B2
DATED : September 16, 2003
INVENTOR(S) : Konfino et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, Item [54] and Column 1, line 1,
Title, change "**COPOLYMER-1 IMPROVEMENTS**" to -- **COPOLYMER-1: IMPROVEMENTS** --

Column 1,
Line 5, change "flied" to -- filed --.

Column 2,
Lines 56 and 57, "chromatographic .. copolymer-1 ....." place on separate line as subheading for Example 1.

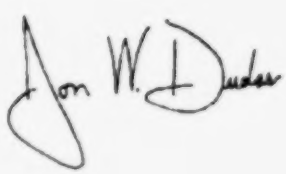
Column 3,
Line 23, change "Analsis" to -- Analysis --

Column 4,
Line 37, change "trifluoroacetyllysine" to -- trifluoroacetyllysine --

Column 6,
Lines 1, 12 and 15, change "Copoloymer" to -- Copolymer --
Line 16, change "purfying" to -- purifying --
Line 28, change "copoloymer" to -- copolymer --
Line 29, change "peperidine" to -- piperidine --

Signed and Sealed this

Ninth Day of November, 2004



JON W. DUDAS
Director of the United States Patent and Trademark Office

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(12) **United States Patent**
Gad et al.

(10) **Patent No.: US 6,800,287 B2**
(45) **Date of Patent: Oct. 5, 2004**

(54) **COPOLYMER 1 RELATED POLYPEPTIDES FOR USE AS MOLECULAR WEIGHT MARKERS AND FOR THERAPEUTIC USE**

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(73) Assignee: **Yeda Research and Development Co., Ltd.**, Rehovot (IL.)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/816,989**

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(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61K 38/16**, A61K 39/00
(52) **U.S. Cl.** **424/185.1**; 530/324
(58) **Field of Search** 424/185.1; 530/324; 514/12

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(57) **ABSTRACT**

The present invention provides molecular weight markers for accurate determination of the molecular weight of glatiramer acetate and other copolymers. The present invention further provides a plurality of molecular weight markers for determining the molecular weight of glatiramer acetate and other copolymers which display linear relationships between molar ellipticity and molecular weight, and between retention time and the log of the molecular weight. The molecular weight markers also optimally demonstrate biological activity similar to glatiramer acetate or corresponding copolymers and can be used for treating or preventing various immune diseases.

10 Claims, 16 Drawing Sheets

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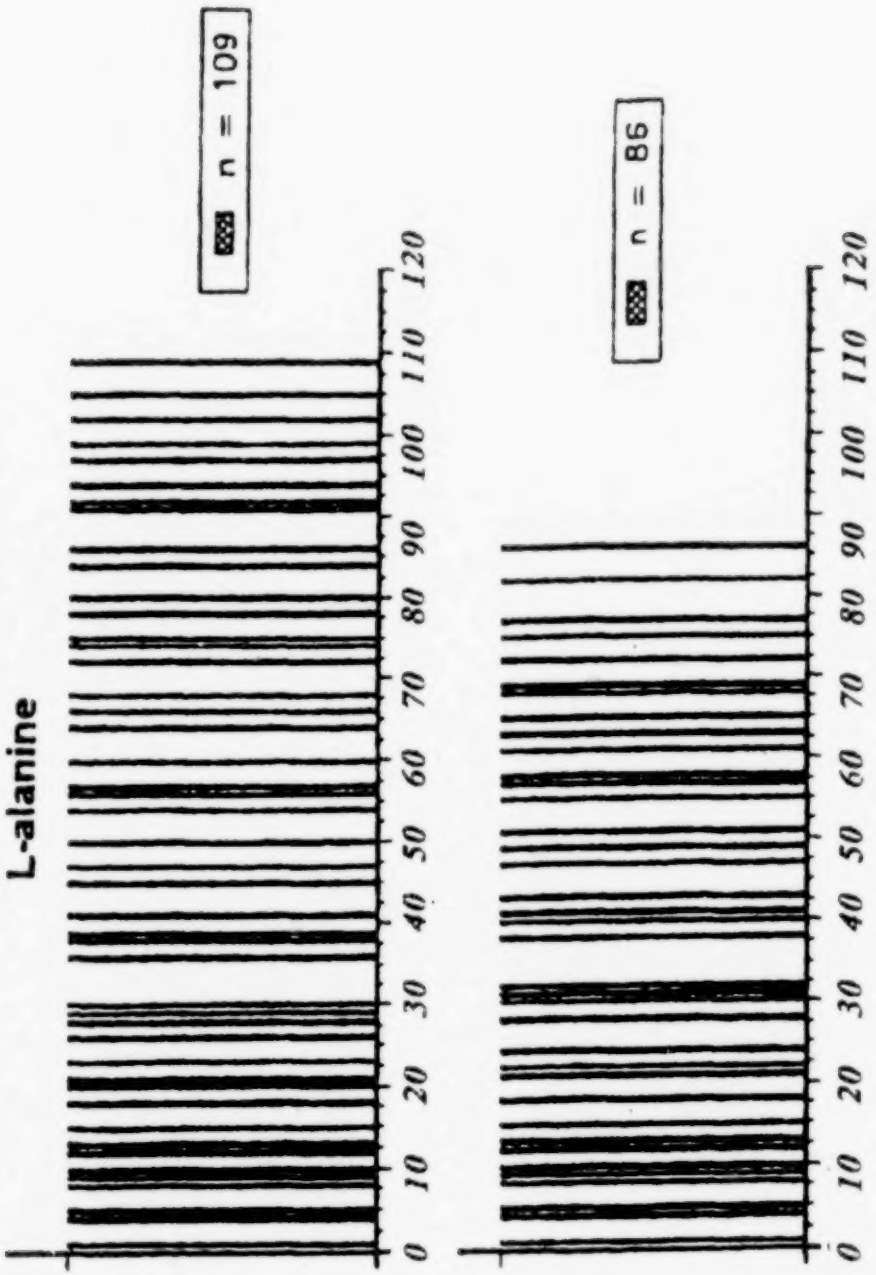

Distribution of L-alanine in the TV-markers
L-alanine
n = 109
n = 86
0 10 20 30 40 50 60 70 80 90 100 110 120
0 10 20 30 40 50 60 70 80 90 100 110 120

FIGURE 1a-1

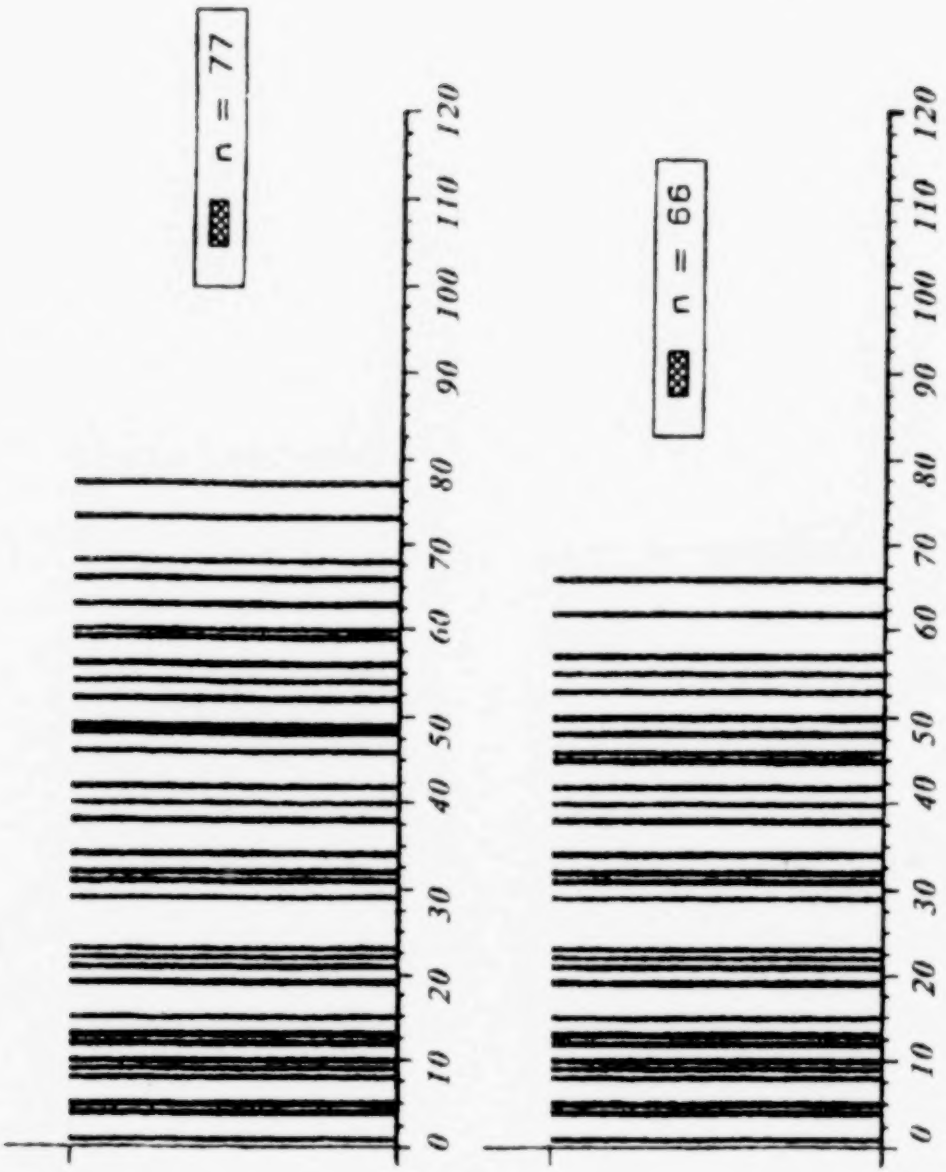
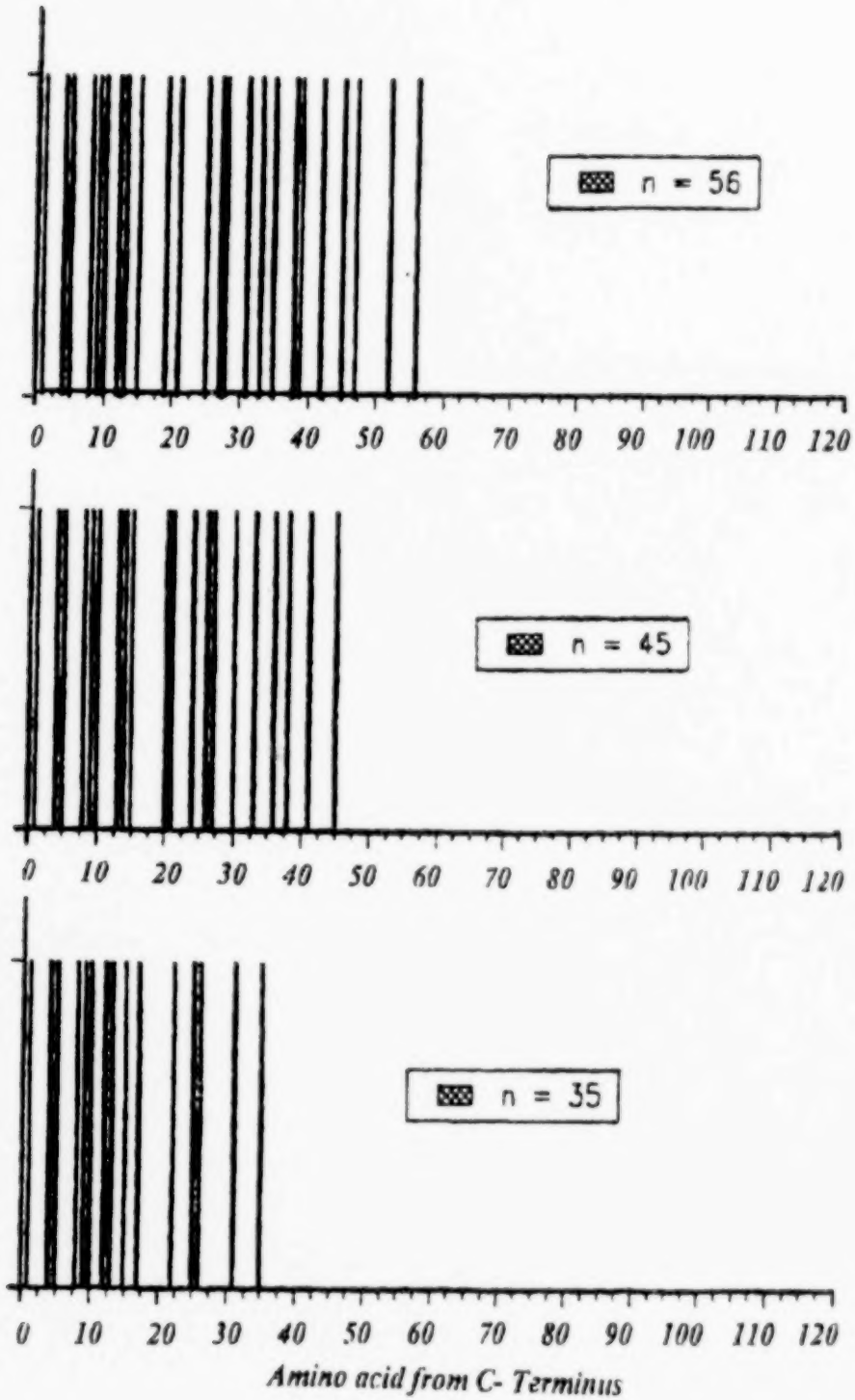
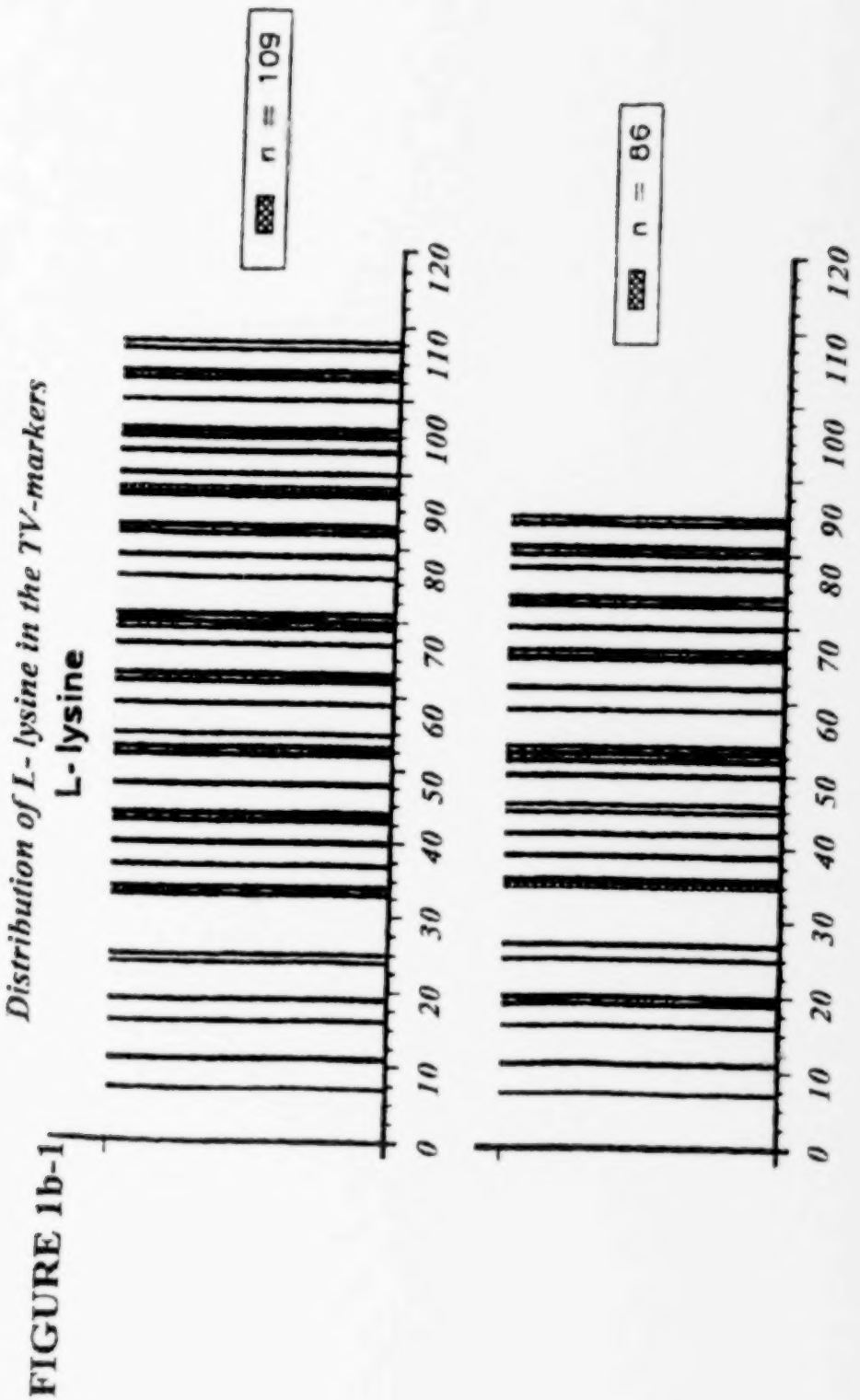

n = 77
0 10 20 30 40 50 60 70 80 90 100 110 120
n = 66
0 10 20 30 40 50 60 70 80 90 100 110 120

FIGURE 1a-2

FIGURE 1a-3


n = 56
0 10 20 30 40 50 60 70 80 90 100 110 120
n = 45
0 10 20 30 40 50 60 70 80 90 100 110 120
n = 35
0 10 20 30 40 50 60 70 80 90 100 110 120
Amino acid from C- Terminus


Distribution of L- lysine in the TV-markers
L- lysine
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n = 86
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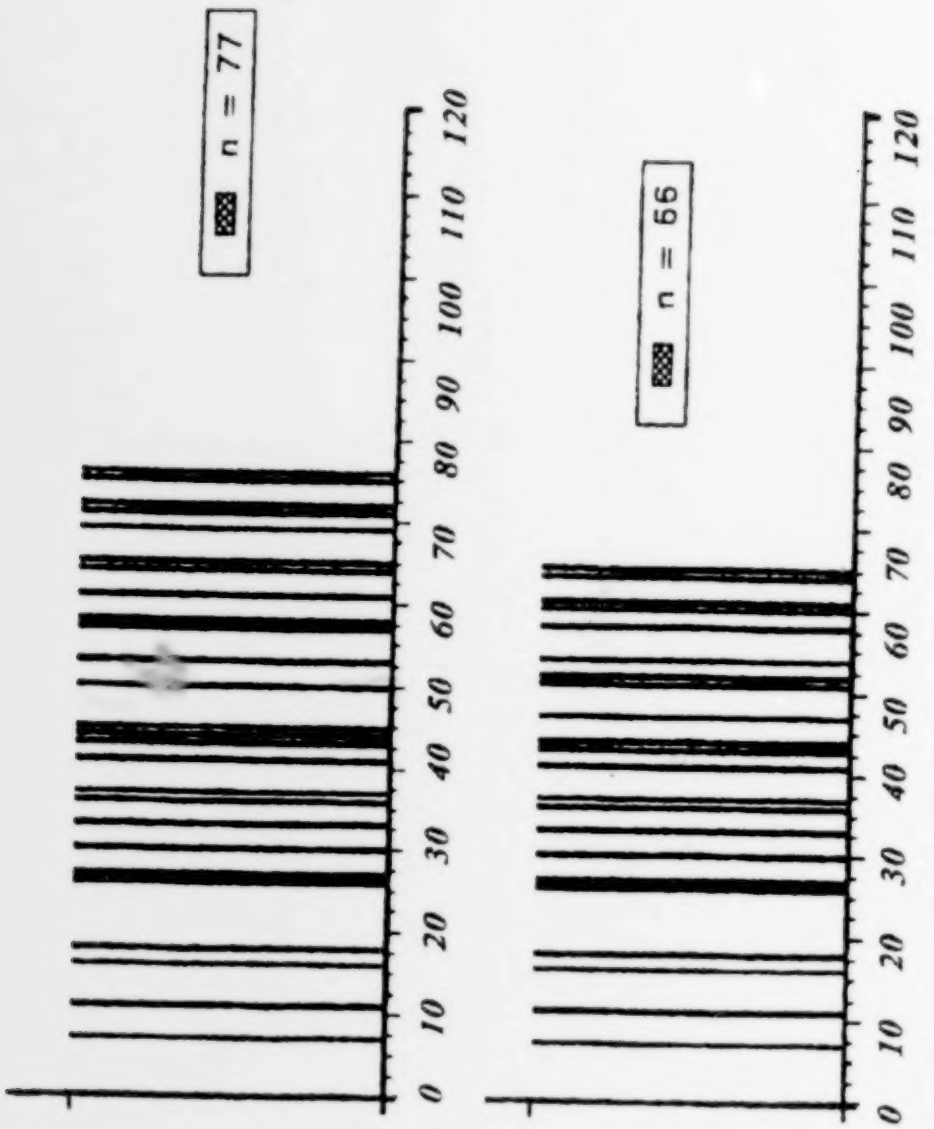
0 10 20 30 40 50 60 70 80 90 100 110 120

FIGURE 1b-1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n = 66
0 10 20 30 40 50 60 70 80 90 100 110 120

FIGURE 1b-2

FIGURE 1b-3

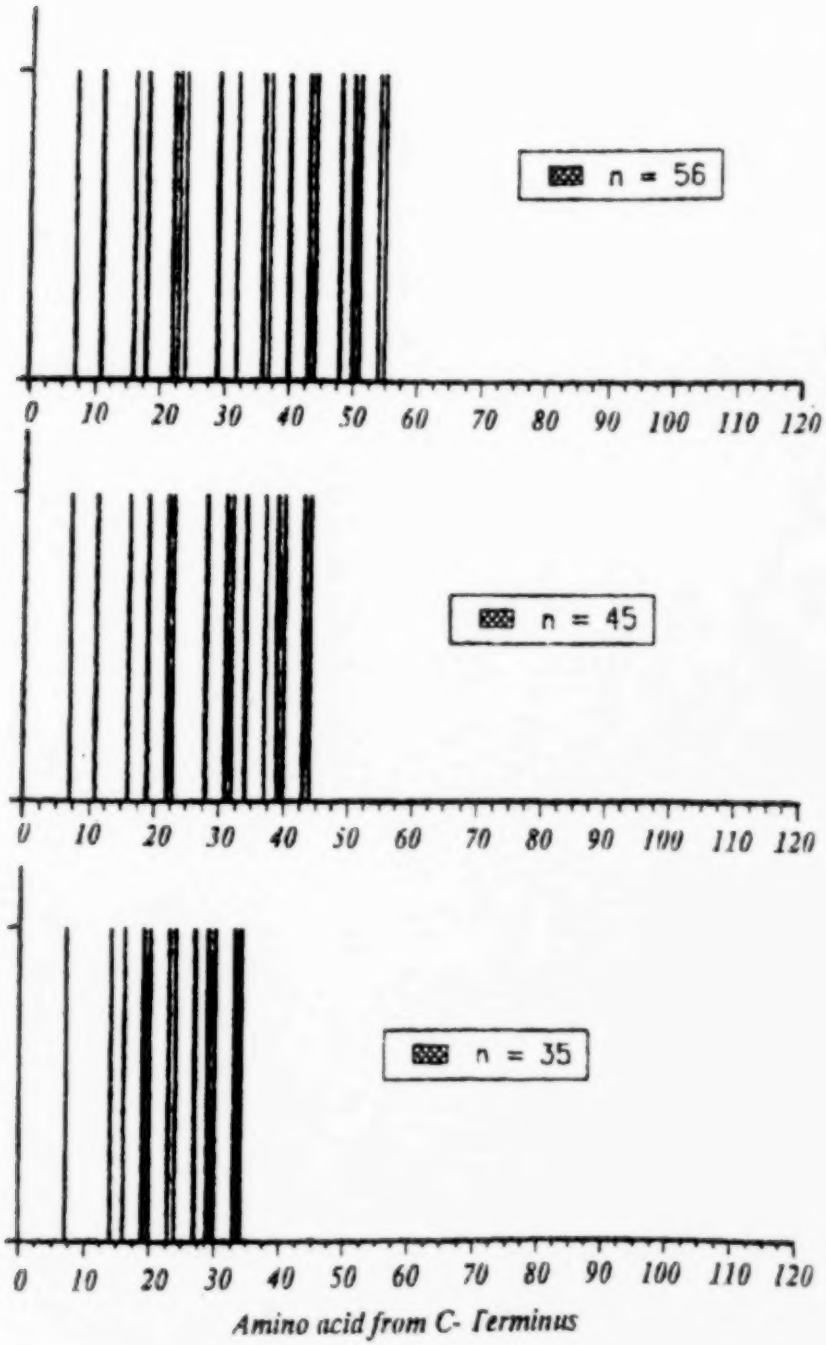
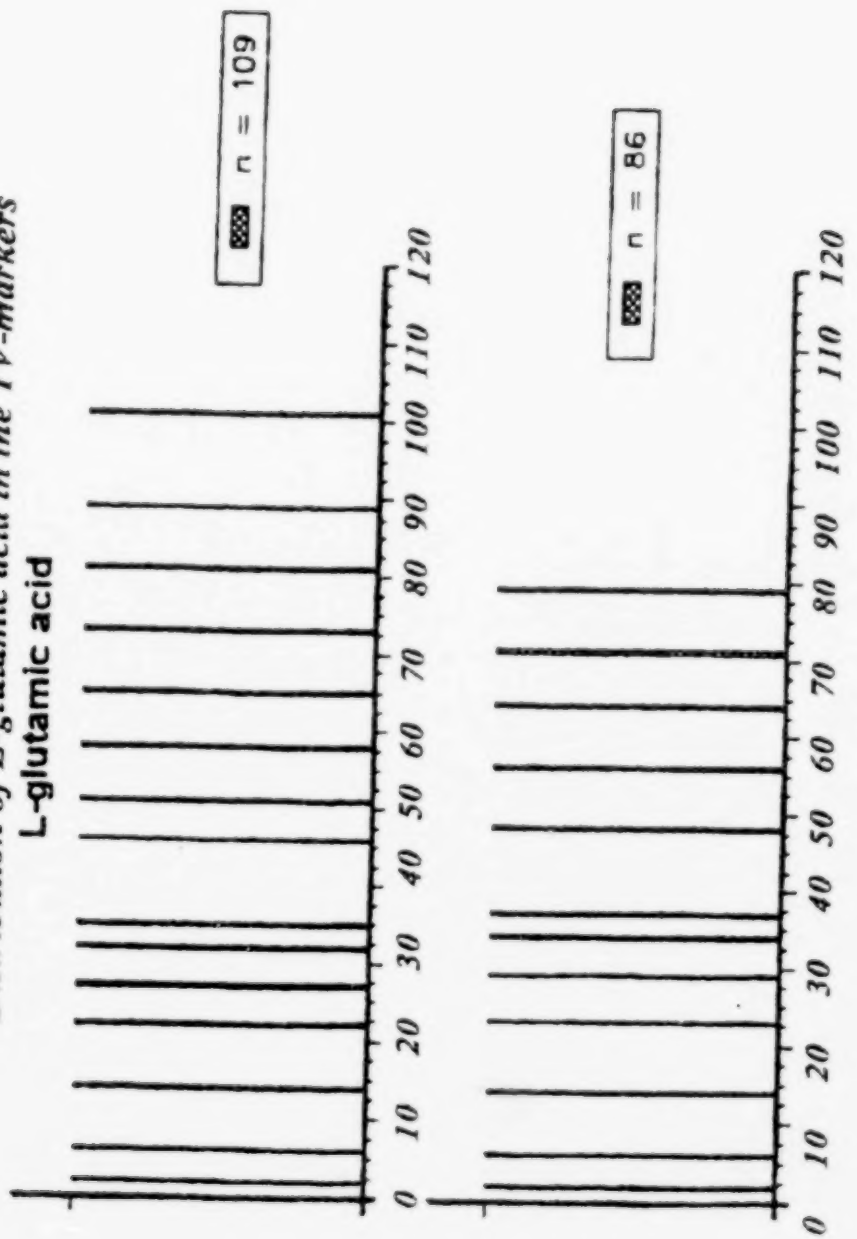
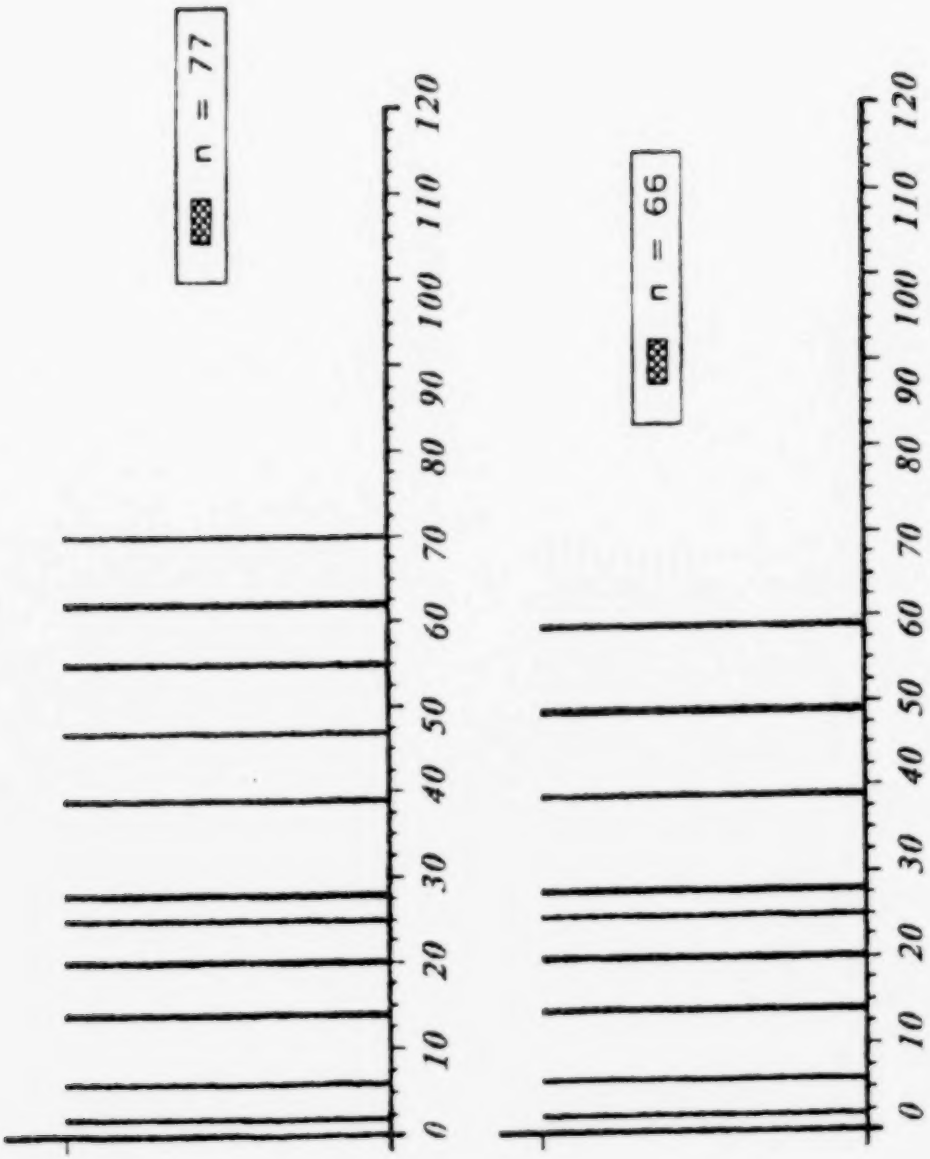

n = 56
0 10 20 30 40 50 60 70 80 90 100 110 120
n = 45
0 10 20 30 40 50 60 70 80 90 100 110 120
n = 35
0 10 20 30 40 50 60 70 80 90 100 110 120
Amino acid from C- Terminus

FIGURE 1c-1


Distribution of L-glutamic acid in the TV-markers
L-glutamic acid
n = 109
n = 86
0 10 20 30 40 50 60 70 80 90 100 110 120
0 10 20 30 40 50 60 70 80 90 100 110 120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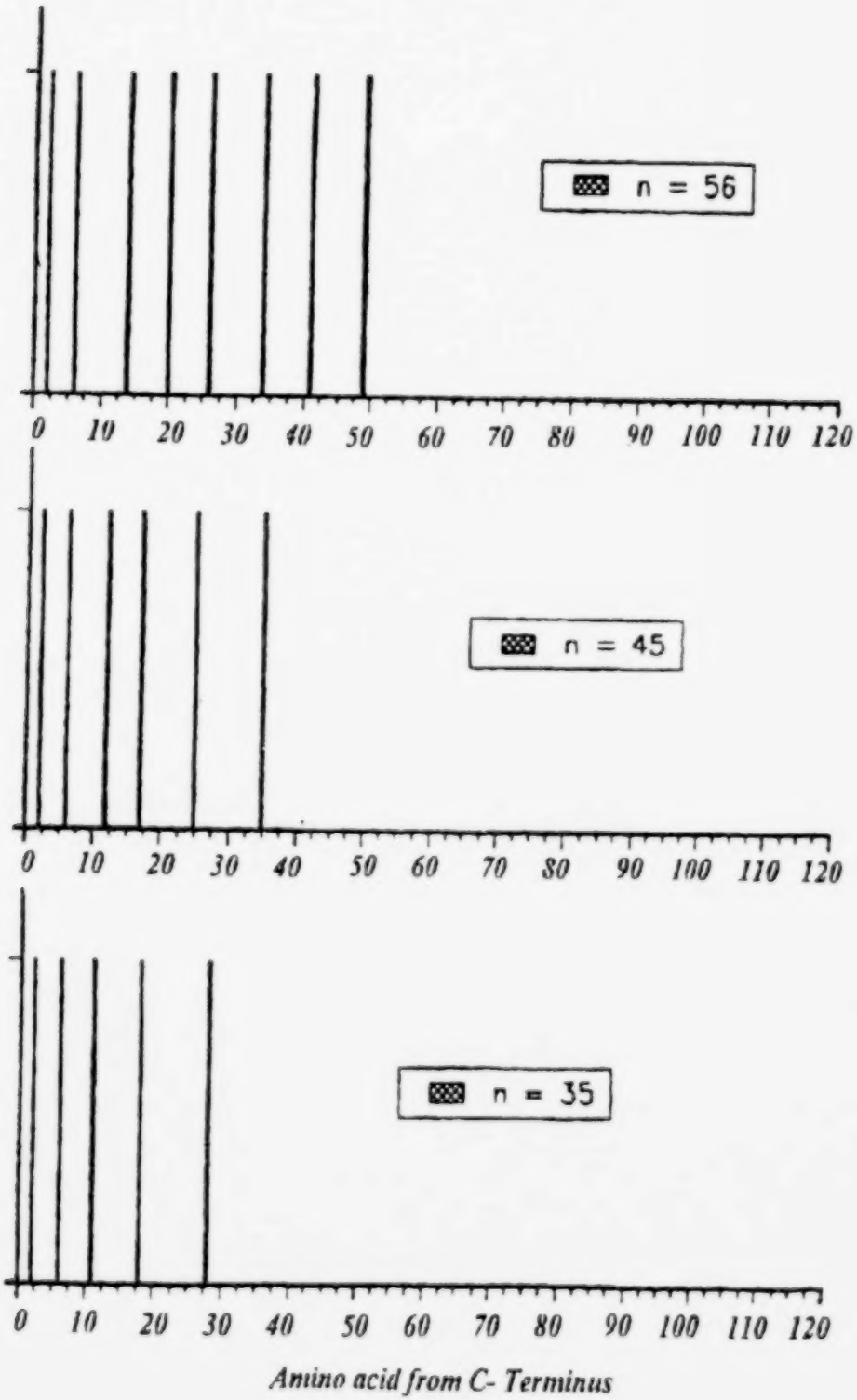
n = 66
0 10 20 30 40 50 60 70 80 90 100 110 120

FIGURE 1c-2

FIGURE 1c-3


n = 56
0 10 20 30 40 50 60 70 80 90 100 110 120
n = 45
0 10 20 30 40 50 60 70 80 90 100 110 120
n = 35
0 10 20 30 40 50 60 70 80 90 100 110 120
Amino acid from C- Terminus

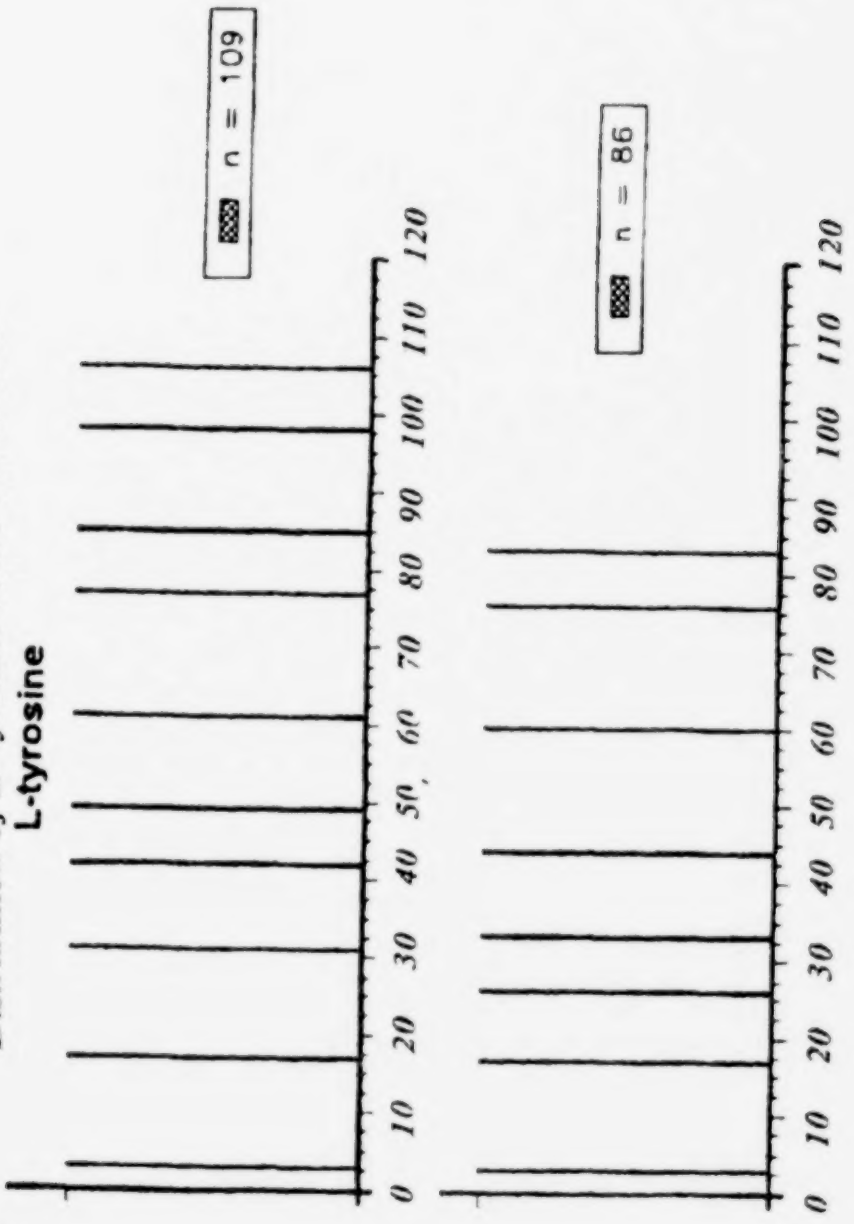
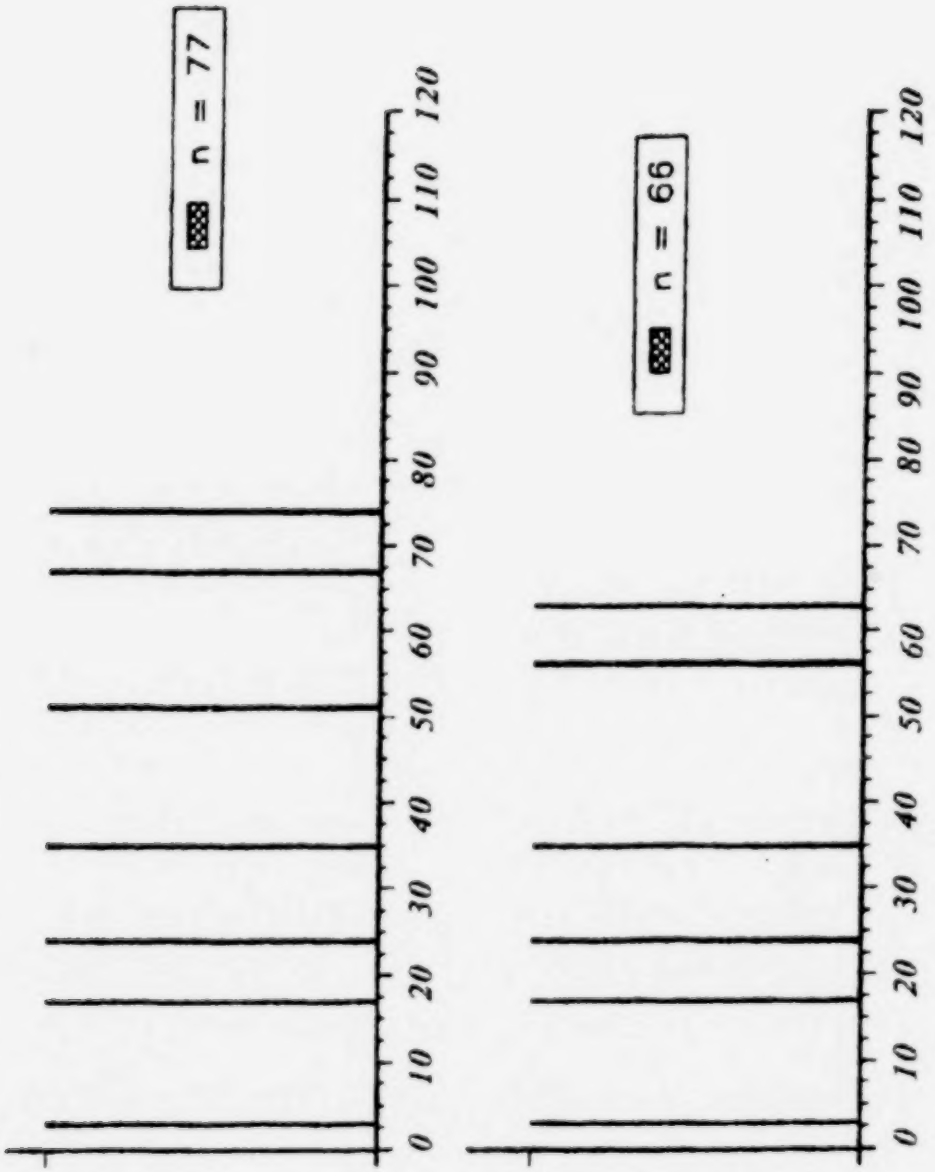

Distribution of L- tyrosine in the TV-markers
L-tyrosine
n = 109
n = 86
0 10 20 30 40 50 60 70 80 90 100 110 120
0 10 20 30 40 50 60 70 80 90 100 110 120

FIGURE 1d-1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0 10 20 30 40 50 60 70 80 90 100 110 120
n = 66
0 10 20 30 40 50 60 70 80 90 100 110 120

FIGURE 1d-2

FIGURE 1d-3

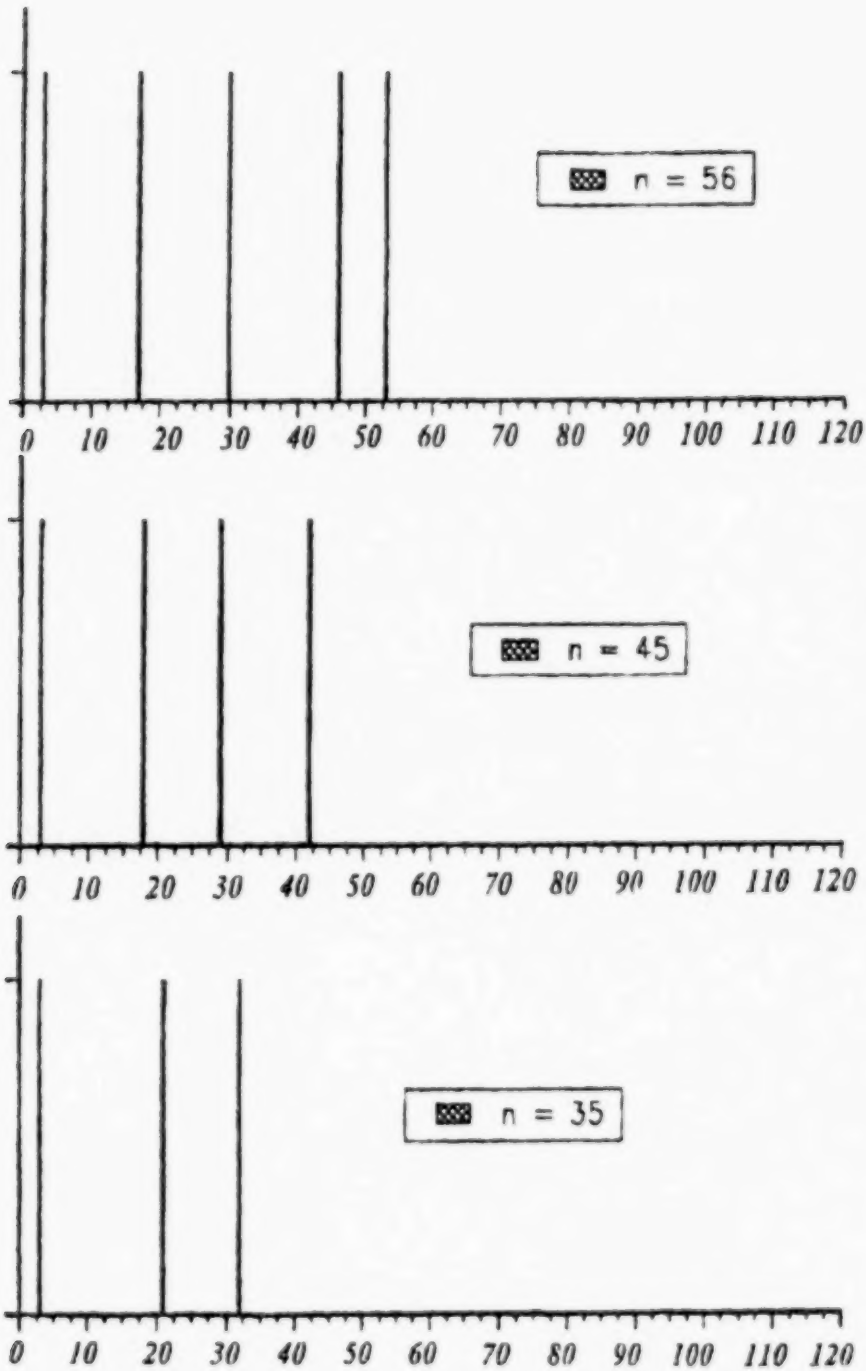

n = 56
n = 45
n = 35
0 10 20 30 40 50 60 70 80 90 100 110 120
Amino acid from C- Terminus

FIGURE 2

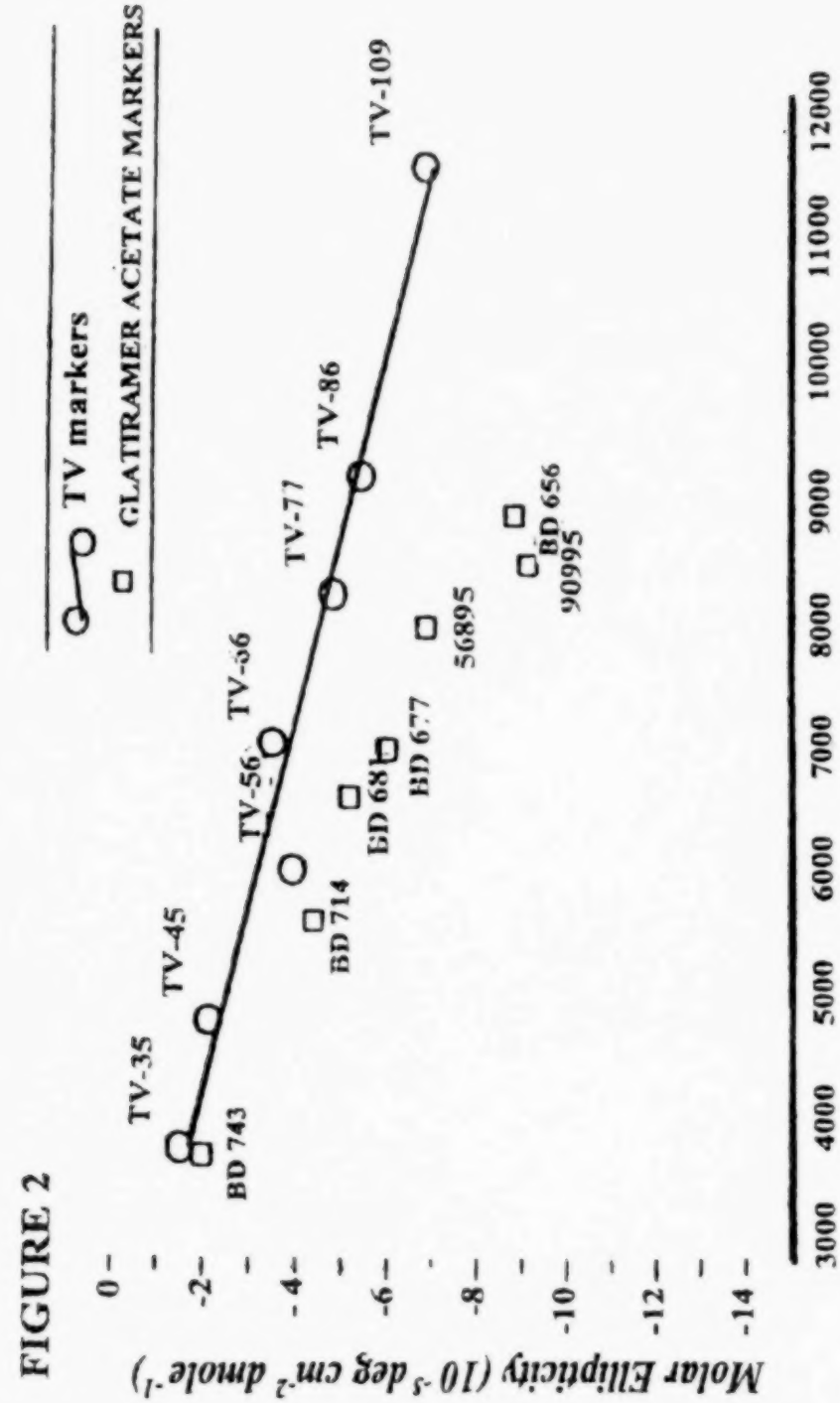

TV markers
GLATIRAMER ACETATE MARKERS
TV-35
TV-45
TV-56
TV-36
TV-77
TV-86
TV-109
BD 743
BD 714
BD 681
BD 677
56895
BD 656
90995
0
-2
-4
-6
-8
-10
-12
-14
3000
4000
5000
6000
7000
8000
9000
10000
11000
12000
Molecular weight (daltons)
Molar Ellipticity (10 -5 deg cm-2 dmole-1)

FIGURE 3a

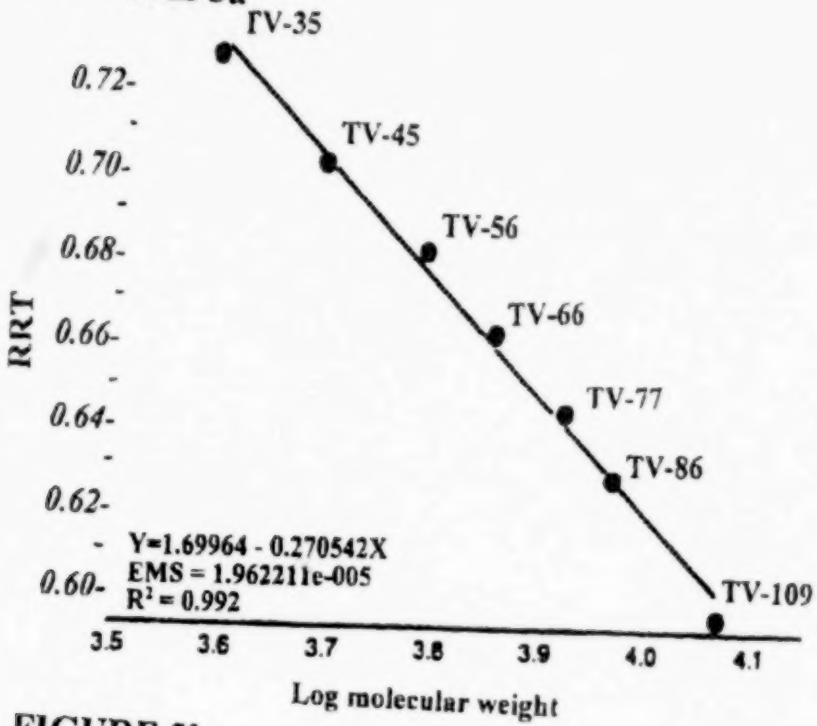


FIGURE 3b

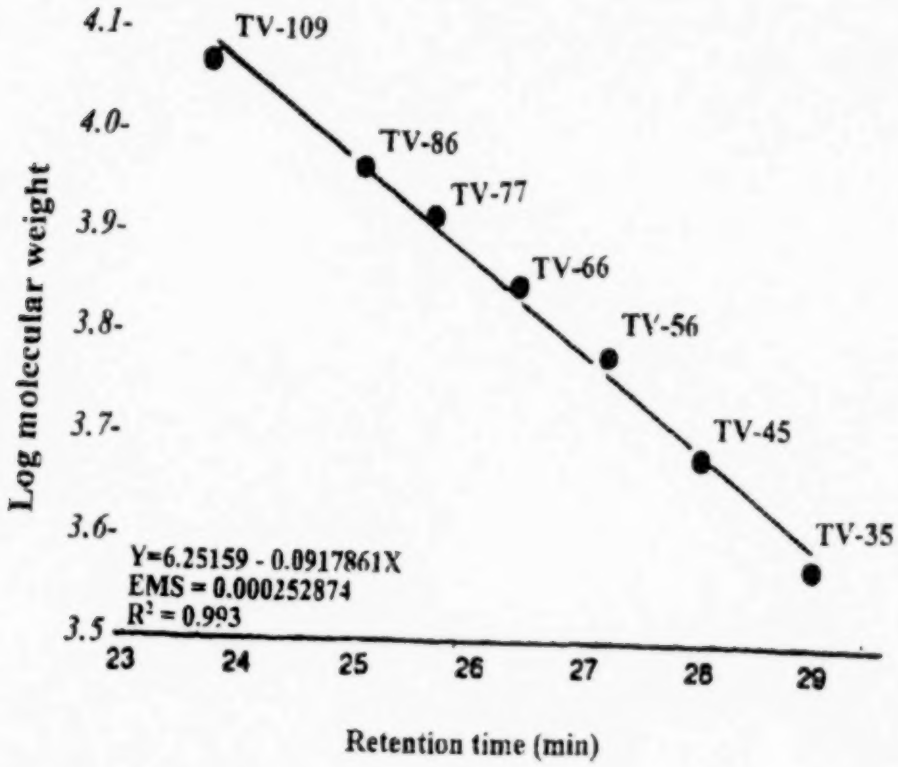


FIGURE 4a

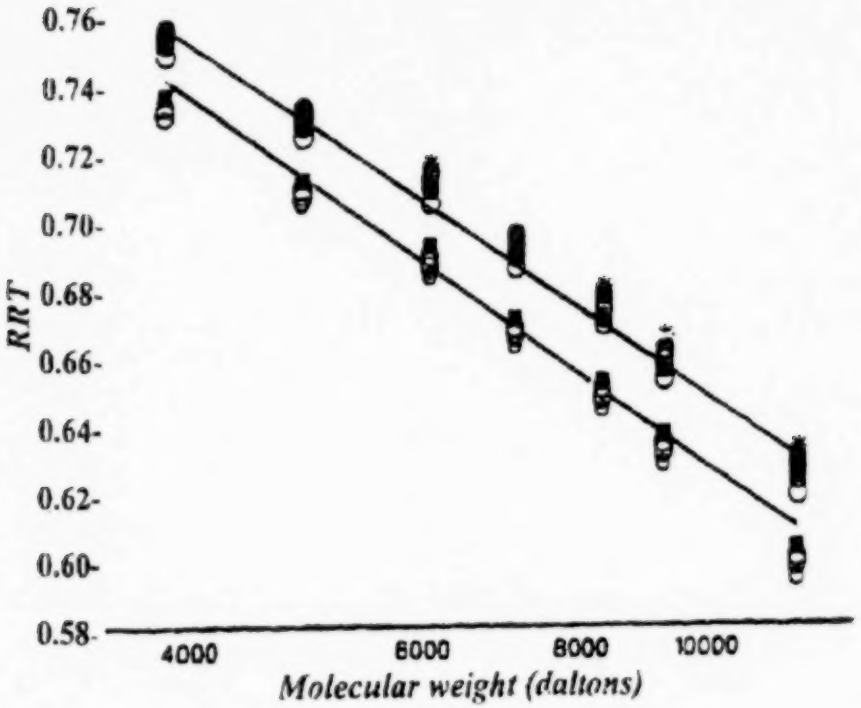
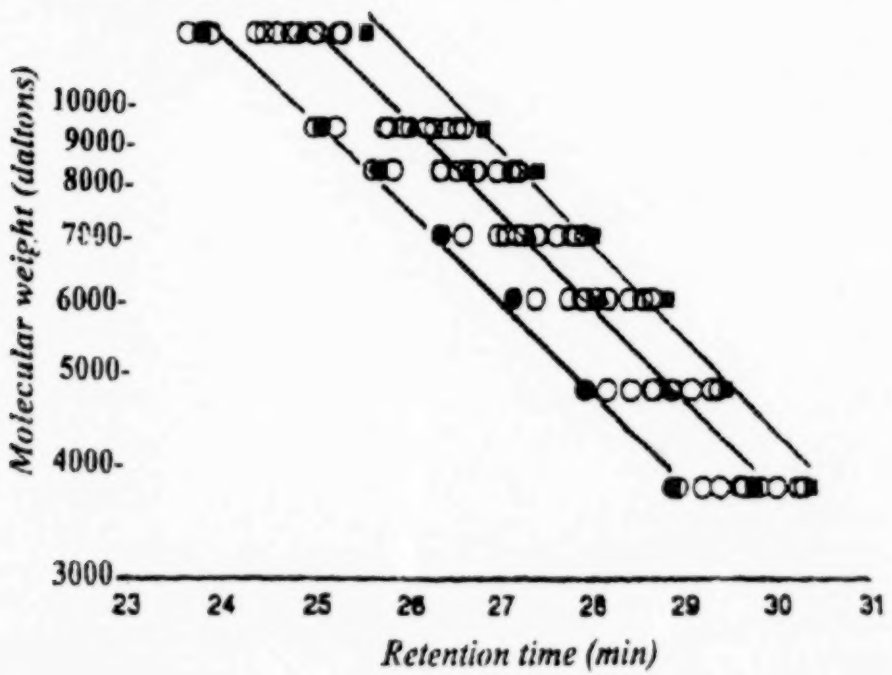


FIGURE 4b



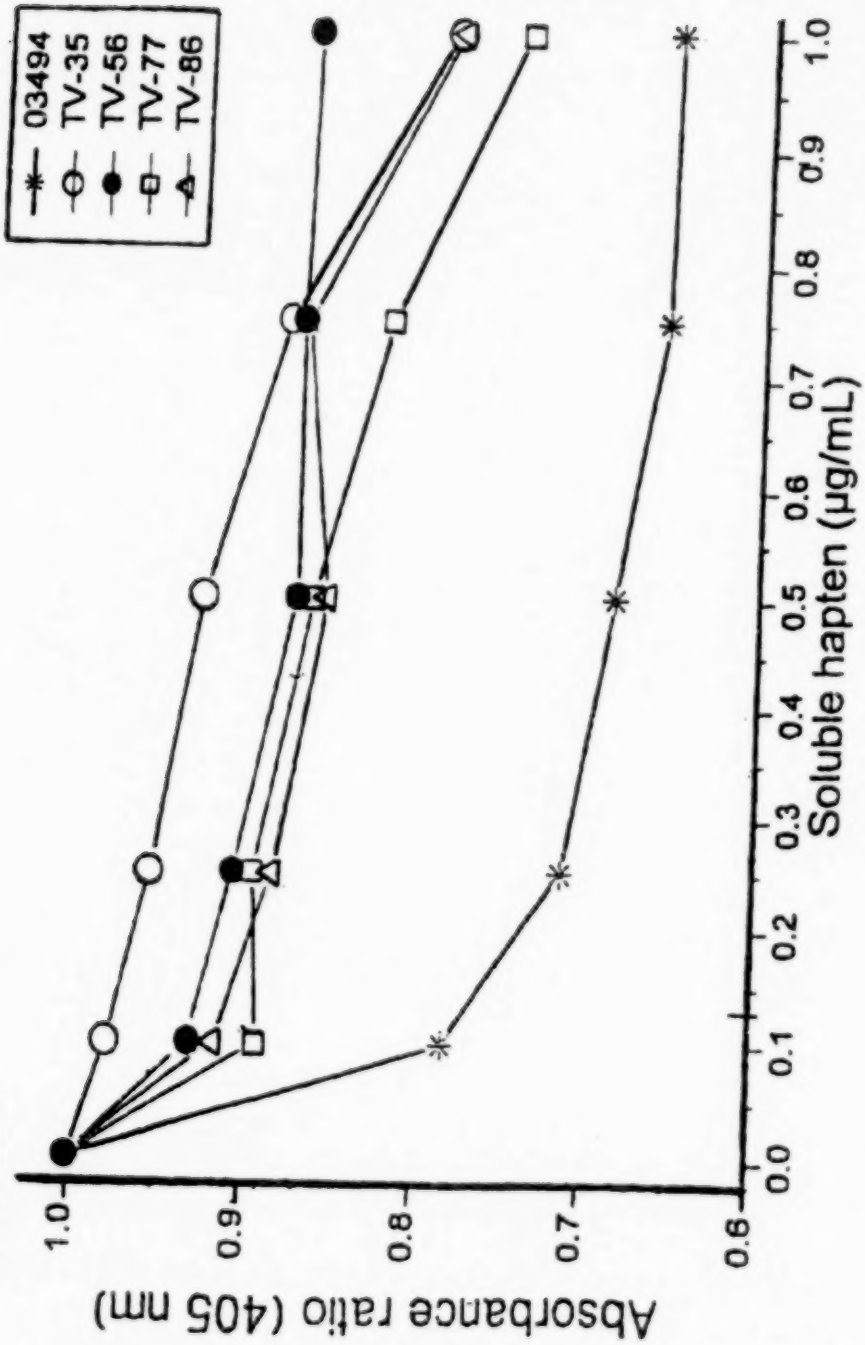

03494
TV-35
TV-56
TV-77
TV-86
Absorbance ratio (405 nm)
1.0
0.9
0.8
0.7
0.6
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Soluble hapten (µg/mL)

FIGURE 5

COPOLYMER 1 RELATED POLYPEPTIDES FOR USE AS MOLECULAR WEIGHT MARKERS AND FOR THERAPEUTIC USE

RELATED APPLICATIONS

This application is a continuation of PCT International Application No. PCT/US99/22402, filed Sep. 24, 1999, designating the United States of America, which claims the priority of U.S. Provisional Application No. 60/101,693, filed Sep. 25, 1998, the contents of which are hereby incorporated by reference into the present application. The present application also claims the benefit of U.S. Provisional Application No. 60/101,825, filed Sep. 25, 1998, which is incorporated by reference herein.

INTRODUCTION

The present invention provides molecular weight markers for accurate determination of the molecular weight of glatiramer acetate, terpolymers and other copolymers. The molecular weight markers are polypeptides having identified molecular weights between about 2,000 daltons and about 40,000 daltons, and an amino acid composition corresponding to glatiramer acetate or a related copolymer. Identified molecular weights are provided by polypeptides having defined sequences. Molecular weight markers corresponding to glatiramer acetate comprise the amino acids alanine, glutamic acid, tyrosine and lysine in specific molar ratios. Molecular weight markers corresponding to related terpolymers comprise three of the four amino acids. In a preferred embodiment, the polypeptide has alanine at the N-terminus and tyrosine at the fourth position from the N-terminus. The present invention further provides a plurality of molecular weight markers for determining the molecular weight range of a copolymer composition. The plurality of molecular weight markers ideally displays linear relationships between molar ellipticity and molecular weight, or between retention time and the log of molecular weight.

Optimally, the polypeptides demonstrate biological activity similar to the copolymer from which they are derived. Polypeptides having defined molecular weights and amino acid compositions similar to glatiramer acetate optimally have therapeutic utility for the treatment of immune diseases and conditions.

BACKGROUND OF THE INVENTION

Autoimmune diseases occur when an organism's immune system fails to recognize some of the organism's own tissues as "self" and attacks them as "foreign." Normally, self-tolerance is developed early by developmental events within the immune system that prevent the organism's own T cells and B cells from reacting with the organism's own tissues. These early immune responses are mediated by the binding of antigens to MHC molecules and presentation to T cell receptors.

This self-tolerance process breaks down when autoimmune diseases develop and the organism's own tissues and proteins are recognized as "autoantigens" and attacked by the organism's immune system. For example, multiple sclerosis is believed to be an autoimmune disease occurring when the immune system attacks the myelin sheath, whose function is to insulate and protect nerves. It is a progressive disease characterized by demyelination, followed by neuronal and motor function loss. Rheumatoid arthritis ("RA") is also believed to be an autoimmune disease which involves chronic inflammation of the synovial joints and infiltration

by activated T cells, macrophages and plasma cells, leading to a progressive destruction of the articular cartilage. It is the most severe form of joint disease. The nature of the autoantigen(s) attacked in rheumatoid arthritis is poorly understood, although collagen type II is a candidate.

A tendency to develop multiple sclerosis and rheumatoid arthritis is inherited. These diseases occur more frequently in individuals carrying one or more characteristic MHC class II alleles. For example, inherited susceptibility for rheumatoid arthritis is strongly associated with the MHC class II DRB 1 *0401, DRB 1*0404, or DRB 1*0405 or the DRB1*0101 alleles. The histocompatibility locus antigens (HLA) are found on the surface of cells and help determine the individuality of tissues from different persons. Genes for histocompatibility locus antigens are located in the same region of chromosome 6 as the major histocompatibility complex (MHC). The MHC region expresses a number of distinctive classes of molecules in various cells of the body, the genes being, in order of sequence along the chromosome, the Class I, II and III MHC genes. The Class I genes consist of HLA genes, which are further subdivided into A, B and C subregions. The Class II genes are subdivided into the DR, DQ and DP subregions. The MHC-DR molecules are the best known; these occur on the surfaces of antigen presenting cells such as macrophages, dendritic cells of lymphoid tissue and epidermal cells. The Class III MHC products are expressed in various components of the complement system, as well as in some non-immune related cells.

A number of therapeutic agents have been developed to treat autoimmune diseases, including steroidal and non-steroidal anti-inflammatory drugs, for example, methotrexate; various interferons; and certain inhibitors of prostaglandin synthesis. However, these agents can be toxic when used for more than short periods of time or cause undesirable side effects. Other therapeutic agents bind to and/or inhibit the inflammatory activity of tumor necrosis factor (TNF), for example, anti-TNF specific antibodies or antibody fragments, or a soluble form of the TNF receptor. These agents target a protein on the surface of a T cell and generally prevent interaction with an antigen presenting cell (APC). However, therapeutic compositions containing natural folded proteins are often difficult to produce, formulate, store, and deliver. Moreover, the innate heterogeneity of the immune system can limit the effectiveness of drugs and complicate long-term treatment of autoimmune diseases.

Glatiramer acetate (Copolymer 1; Cop 1; hereinafter GLAT copolymer) is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 4.6:1.5:3.6:1.0, respectively, which is synthesized by chemically polymerizing the four amino acids, forming products with average molecular weights ranging from about 4000 to about 13,000 daltons. The corresponding molar fractions are approximately 0.427 for alanine, 0.141 for glutamic acid, 0.337 for lysine and 0.093 for tyrosine, and may vary by about +/−10%. Related copolymers are mixtures of polypeptides composed of three (thus, "terpolymers") of the four aforementioned amino acids. Copolymer 1 and the terpolymers address the innate heterogeneity of the mammalian immune system and human population and are effective for treatment of autoimmune diseases and other immune conditions. Preferred average molecular weight ranges and processes of making terpolymers are described in U.S. Pat. No. 5,800,808, which is hereby incorporated by reference in its entirety. Also contemplated by the invention are other copolymers comprised of other combinations of three, four, or five or more amino acids.

To certify a Copolymer 1 or terpolymer preparation for use in a pharmaceutical products, it is necessary to accurately determine the molecular weight distribution of the polypeptides in the preparation. One method for determining the molecular weight is chromatography on a Superose 12 column. Calibration coefficients of columns for determination of glatiramer acetate molecular weight have been determined using glatiramer acetate batches with indirectly measured molecular weights. Indirect measures have included viscosimetry and velocity-sedimentation ultracentrifugation. More recently, batches of glatiramer acetate markers have been prepared whose molecular weights were determined by multiple angle laser light scattering (MALLS).

Thus, a need exists for molecular weight markers useful as standards for determining the molecular weight distribution of copolymer compositions contemplated by the invention. Desirable molecular weight markers have defined molecular weights and physical properties which are analogous to the molecules for which molecular weight is to be determined. Ideally, there is a linear relationship between the defined molecular weights (or the log of the defined molecular weights) of the markers and a measurable physical property such as, for example, the molar ellipticity of the markers, or the retention time of the markers on a molecular sizing column.

SUMMARY OF THE INVENTION

Sequence-defined molecular weight markers that have chemical and physical characteristics similar to GLAT copolymer provide an accurate and robust calibration set for determinations of molecular weight of production batches. The present invention provides derivatives of GLAT copolymer useful as molecular weight markers for determining the molecular weight ranges of GLAT copolymer preparations and optimally having therapeutic utility for treatment of immune conditions. The invention further provides polypeptides having defined molecular weights which are derivatives of other copolymers and which are useful for determining molecular weight ranges of preparations of those copolymers. When those copolymers are therapeutically useful, the derivative polypeptides optimally have therapeutic utility. For determination of the molecular weight range of a GLAT copolymer preparation, the preferred derivative is a polypeptide having an amino acid composition corresponding approximately to GLAT copolymer and an identified molecular weight which is between about 2,000 daltons and about 40,000 daltons. The polypeptide preferably has specific molar ratios of amino acids alanine, glutamic acid, tyrosine and lysine. Moreover, in a preferred embodiment the polypeptide has alanine at the N-terminus and tyrosine at the fourth position from the N-terminus. For determination of the molecular weight of a terpolymer, the preferred derivative will have a defined molecular weight and an amino acid composition corresponding approximately to that of the terpolymer. Other copolymers are also contemplated by the invention. When determining of the molecular weight of a copolymer contemplated by the invention, the polypeptide derivative will have a defined molecular weight and an amino acid composition corresponding approximately to that of the copolymer.

The present invention further provides a plurality of molecular weight markers for determining the molecular weight of glatiramer acetate or a terpolymer or other copolymer on a molecular weight sizing column. The markers comprise two to ten or more polypeptides, each polypeptide having an identified molecular weight. When determining the molecular weight range of glatiramer acetate, a preferred plurality of molecular weight markers will have defined molecular weights from about 2,000 daltons to about 40,000 daltons, and amino acid compositions corresponding to glatiramer acetate or a selected terpolymer. In preferred embodiments, there is a linear relationship between the log molecular weight of the polypeptide molecular weight markers and either the retention time of the molecular weight markers on a sizing column or between the molecular weight of the molecular weight markers and the molar ellipticity of the molecular weight markers.

The present invention further provides pharmaceutical compositions which include a therapeutically effective amount of a polypeptide useful as a molecular weight marker for determining the molecular weight range of GLAT copolymer and consisting essentially of amino acids alanine, glutamic acid, tyrosine and lysine in molar fractions of from about 0.38 to about 0.50 alanine, from about 0.13 to about 0.15 glutamic acid, from about 0.08 to about 0.10 tyrosine, and from about 0.3 to about 0.4 lysine, and a pharmaceutically acceptable carrier.

The present invention further provides pharmaceutical compositions which include a therapeutically effective amount of a polypeptide useful as a molecular weight marker for determining the molecular weight range of a terpolymer and consisting essentially of amino acids alanine, tyrosine, and lysine in the molar fractions of from about 0.3 to about 0.6 alanine, from about 0.005 to about 0.25 tyrosine, and from about 0.1 to about 0.5 lysine, and a pharmaceutically acceptable carrier. The polypeptide is preferably substantially free of glutamic acid.

The present invention further provides pharmaceutical compositions which include a therapeutically effective amount of a polypeptide useful as a molecular weight marker for determining the molecular weight range of a terpolymer and consisting essentially of glutamic acid, tyrosine and lysine in molar fractions of from about 0.005 to about 0.300 glutamic acid, from about 0.005 to about 0.250 tyrosine, and from about 0.3 to about 0.7 lysine, and a pharmaceutically acceptable carrier. The polypeptide is preferably substantially free of alanine.

The present invention further provides pharmaceutical compositions which include a therapeutically effective amount of a polypeptide useful as a molecular weight marker for determining the molecular weight range of a terpolymer and consisting essentially of amino acids alanine, glutamic acid and tyrosine in molar fractions of from about 0.005 to about 0.8 alanine, from about 0.005 to about 0.3 glutamic acid, and from about 0.005 to about 0.25 tyrosine, and a pharmaceutically acceptable carrier. The polypeptide is preferably substantially free of lysine.

The present invention also provides pharmaceutical compositions which includes a therapeutically effective amount of a polypeptide useful as a molecular weight marker for determining the molecular weight range of a terpolymer and consisting essentially of alanine, glutamic acid and lysine, in molar fractions of from about 0.005 to about 0.6 alanine, from about 0.005 to about 0.3 glutamic acid, and from about 0.2 to about 0.7 lysine, and a pharmaceutically acceptable carrier. The polypeptide is preferably substantially free of tyrosine.

In general, pharmaceutical compositions of the invention include therapeutically effective amounts of a polypeptide which is useful as a molecular weight marker for determining the molecular weight range of a copolymer of any number (e.g., three to five or more) of amino acids. In the manner of glatiramer acetate, such a copolymer is a diverse

population of sequences of the amino acids. The polypeptide useful as a molecular weight marker consists of those amino acids in molar fractions corresponding approximately to the copolymer.

The present invention further provides methods for treating and preventing immune-mediated and autoimmune diseases in a mammal which include administering a therapeutically effective amount of a molecular weight marker of the invention. In another embodiment, the method for treating immune-mediated and autoimmune diseases in a mammal further involves inhibiting proliferation of T cells involved in the immune attack. In another embodiment, the method for treating immune-mediated and autoimmune diseases in a mammal involves binding a molecular weight marker of the invention to an antigen presenting cell. In yet another embodiment, the method for treating immune-mediated and autoimmune disease in a mammal involves binding a molecular weight marker of the invention to a major histocompatibility complex class II protein which is associated with autoimmune diseases.

Autoimmune diseases contemplated by the present invention include arthritic conditions, demyelinating diseases and inflammatory diseases. For example, autoimmune diseases which can be treated by the present compositions include multiple sclerosis, rheumatoid arthritis, osteoarthritis, autoimmune hemolytic anemia, autoimmune oophoritis, autoimmune thyroiditis, autoimmune uveoretinitis, Crohn's disease, chronic immune thrombocytopenic purpura, colitis, contact sensitivity disease, diabetes mellitus, Graves disease, Guillain-Barre's syndrome, Hashimoto's disease, idiopathic myxedema, myasthenia gravis, psoriasis, pemphigus vulgaris, or systemic lupus erythematosus.

Immune-mediated diseases result from undesired sensitivity of the immune system to particular foreign antigens. Examples are host-versus-graft disease (HVGD) and graft-versus-host disease (GVHD) and numerous types of delayed-type hypersensitivity (DTH).

The present compositions can be used to treat one or more of these diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1*a*-1, 1*a*-2 and 1*a*-3 provide the distribution of alanine in the molecular markers (TV-markers) described in Table 1. The amino acid position is defined by the X-axis. The presence of an alanine is indicated by a vertical bar at the indicated amino acid position.

FIGS. 1*b*-1, 1*b*-2 and 1*b*-3 provide the distribution of lysine in the TV-markers described in Table 1. The amino acid position is defined by the X-axis. The presence of a lysine residue is indicated by a vertical bar at the indicated amino acid position.

FIGS. 1*c*-1, 1*c*-2 and 1*c*-3 provide the distribution of glutamic acid in the TV-markers described in Table 1. The amino acid position is defined by the X-axis. The presence of a glutamic acid residue is indicated by a vertical bar at the indicated amino acid position.

FIGS. 1*d*-1, 1*d*-2 and 1*d*-3 provide the distribution of tyrosine in the TV-markers described in Table 1. The amino acid position is defined by the X-axis. The presence of a tyrosine residue is indicated by a vertical bar at the indicated amino acid position.

FIG. 2 provides a plot of the molar ellipticity versus molecular weight of the present TV-markers compared to known glatiramer acetate markers. The molar ellipticity is provided in 10^{-5} deg cm^{-2} $dmole^{-1}$ and the molecular weight is in daltons. Circles indicate TV-markers and squares depict glatiramer acetate markers. As shown, the TV-markers provide a linear relationship between molar ellipticity and molecular weight.

FIG. 3*a* provides a plot of the relative retention time (RRT) of the present TV-markers versus the log molecular weight of those markers, using the RRT-based algorithm.

FIG. 3*b* provides a plot of the log molecular weight of the TV-markers versus the retention time (RT) of those markers, using the Millennium-based algorithm.

FIG. 4*a* provides a plot summarizing several calibrations of the relative retention time (RRT) of the present TV-markers versus the molecular weight of those markers, using the RRT-based algorithm. Data were obtained from sixteen columns. Average values for each of the sixteen calibrations are depicted.

FIG. 4*b* provides a plot summarizing several calibrations of the molecular weight of the TV-markers versus the relative retention time (RRT) of those markers, using the Millennium-based algorithm. Data were obtained from sixteen columns. Average values for each of the sixteen calibrations are depicted.

FIG. 5 depicts inhibition of Cop 1 binding to anti-Cop 1 polyclonal antibodies by four TV-markers and Cop 1 (03494). Absorbance ratio indicates absorbance measured with increasing inhibitor concentration relative to absorbance in the absence of binding inhibition.

DETAILED DESCRIPTION OF THE INVENTION

Molecular weight markers of the invention (e.g., TV-markers), include polypeptides having an amino acid composition approximately corresponding to glatiramer acetate or related terpolymers, and an identified molecular weight which is between about 2,000 daltons and about 40,000 daltons and are useful for accurately determining the molecular weight of GLAT copolymer and related terpolymers. It follows from the requirement for an identified molecular weight that a TV-marker should have a discrete molecular weight and not a range of molecular weights. Accordingly, TV-markers are synthesized according to a predetermined amino acid sequence which corresponds in composition to the copolymer for which molecular weight range is to be determined. Optimally, TV-markers have therapeutic activity which is similar to corresponding copolymer. These markers can be used in any molecular size discrimination system using any available molecular weight determination procedure or apparatus. For example, the present markers can be used for calibration of any chromatographic procedure or apparatus which is used for molecular weight determinations of polypeptides or proteins. Such a chromatographic apparatus can be a molecular weight sizing column which separates polypeptides on the basis of their molecular size. Examples of molecular weight sizing columns include TSK columns, Sephadex columns, Sepharose columns, and Superose columns. In order to provide molecular weight markers of discrete size and composition, molecular weight markers of the invention can be synthesized according to predetermined sequences by methods which are well known to those of skill in the art.

Amino acids of the present invention include, but are not limited to the 20 commonly occurring amino acids. Also included are naturally occurring and synthetic derivatives, for example, selenocysteine. Amino acids further include amino acid analogues. An amino acid "analogue" is a chemically related form of the amino acid having a different

configuration, for example, an isomer, or a D-configuration rather than an L-configuration, or an organic molecule with the approximate size and shape of the amino acid, or an amino acid with modification to the atoms that are involved in the peptide bond, so as to be protease resistant when polymerized in a peptide or polypepide.

The phrases "amino acid" and "amino acid sequence" as defined here and in the claims can include one or more components which are amino acid derivatives and/or amino acid analogs comprising part or the entirety of the residues for any one or more of the 20 naturally occurring amino acids indicated by that sequence. For example, in an amino acid sequence having one or more tyrosine residues, a portion of one or more of those residues can be substituted with homotyrosine. Further, an amino acid sequence having one or more non-peptide or peptidomimetic bonds between two adjacent residues, is included within this definition.

The one letter and three letter amino acid codes (and the amino acid that each represents) are as follows: A means ala (alanine); C means cys (cysteine); D means asp (aspartic acid); E means glu (glutamic acid); F means phe (phenylalanine); G means gly (glycine); H means his (histidine); I means ile (isoleucine); K means lys (lysine); L means leu (leucine); M means met (methionine); N means asn (asparagine); P means pro (proline); Q means gin (glutamine); R means arg (arginine); S means ser (serine); T means thr (threonine); V means val (valine); W means trp (tryptophan); and Y means tyr (tyrosine).

The term "hydrophobic" amino acid is defined here and in the claims as including aliphatic amino acids alanine (A, or ala), glycine (G, or gly), isoleucine (I, or ile), leucine (L, or leu), proline (P, or pro), and valine (V, or val), the terms in parentheses being the one letter and three letter standard code abbreviation s for each amino acid, and aromatic amino acids tryptophan (W, or trp), phenylalanine (F or phe), and tyrosine (Y, or tyr). The amino acids confer hydrophobicity as a function of the length of aliphatic and size of aromatic side chains, when found as residues within a protein.

The term "charged" amino acid is defined here and in the claims as including an amino acids aspartic acid (D, or asp), glutamic acid (E, or glu), histidine (H, or his), arginine (R, or arg) and lysine (K, or lys), which confer a positive (his, lys and arg) or negative (asp and gly) charge at physiological values of pH in aqueous solutions on proteins containing these residues.

Polypeptide Compositions Contemplated by the Invention—According to the present invention, polypeptides having defined molecular weights and comprising three or all four of the amino acids tyrosine, glutamic acid, alanine and lysine are preferred for the present markers. However, one of skill in the art can readily substitute structurally-related amino acids without deviating from the spirit of the invention. Thus, the present invention further contemplates conservative amino acid substitutions for tyrosine, glutamic acid, alanine and lysine in the present polypeptides. Such structurally-related amino acids include those amino acids which have about the same charge, hydrophobicity and size as tyrosine, glutamic acid, alanine or lysine. For example, lysine is structurally-related to arginine and histidine; glutamic acid is structurally-related to aspartic acid; tyrosine is structurally-related to serine, threonine, tryptophan and phenylalanine; and alanine is structurally-related to valine, leucine and isoleucine.

Moreover, molecular weight markers of the invention can be composed of L- or D-amino acids. As is known by one of skill in the art, L-amino acids occur in most natural proteins. However, D-amino acids are commercially available and can be substituted for some or all of the amino acids used to make molecular weight markers of the invention. The present invention contemplates molecular weight markers formed from mixtures of D- and L-amino acids, as well as molecular weight markers consisting essentially of either L- or D-amino acids.

The average molecular weight and the average molar fraction of the amino acids in the present polypeptides can vary. However, a molecular weight range of about 2,000 to about 40,000 is contemplated, and basic polypeptides, rather than acidic polypeptides, are preferred.

In one embodiment, the present invention provides polypeptide markers containing tyrosine, alanine, glutamic acid and lysine in defined molar ratios. In a more preferred embodiment, the molar ratio of amino acids of the present polypeptides is that found in GLAT copolymer. Such a correspondence in molar ratios provides the best molecular weight markers because those markers will have a charge and a molecular shape which is similar to that of GLAT copolymer. When structurally dissimilar markers are used, the markers may migrate or elute somewhat differently from GLAT copolymer preparations, even though those preparations have the same molecular weight as the markers.

Moreover, in a preferred embodiment, alanine is at the N-terminus and tyrosine is at position four from the N-terminus. Edman degradation analyses performed on various glatiramer acetate batches revealed a greater abundance of alanine at the N-terminus and tyrosine at position four from the N-terminus. Therefore, in certain preferred embodiments, GLAT copolymer molecular weight markers have alanine at the N-terminus and tyrosine at position four from the N-terminus. Studies of the polymerization reaction used to synthesize GLAT copolymer have indicated that alanine and glutamic acid polymerize faster than lysine. As a result, the C-terminal portion of GLAT copolymer tends to be richer in alanine and glutamic acid, whereas the N-terminal portion tends to be richer in lysine. In preferred embodiments, the distribution of amino acid residues in GLAT copolymer molecular weight markers reflects this bias.

When determining the molecular weight range of GLAT copolymer, a preferred molecular weight marker consists essentially of amino acids alanine, glutamic acid, tyrosine and lysine in molar fractions of from about 0.38 to about 0.50 alanine, from about 0.13 to about 0.15 glutamic acid, from about 0.08 to about 0.10 tyrosine, and from about 0.3 to about 0.4 lysine.

In other embodiments, the present invention provides molecular weight markers containing three of the four amino acids alanine, glutamic acid, tyrosine, and lysine in defined ratios. In preferred embodiments, the molar fractions of amino acids present the molecular weight markers correspond to that found in a corresponding terpolymer.

When the molecular weight marker contains alanine, glutamic acid and tyrosine, alanine can be present in a mole fraction of about 0.005 to about 0.800, glutamic acid can be present in a mole fraction of about 0.005 to about 0.300, and tyrosine can be present in a mole fraction of about 0.005 to about 0.250. The molecular weight is from about 2,000 to about 40,000 daltons, and preferably from about 3000 to about 12,000 daltons.

When the molecular weight marker contains alanine, glutamic acid and lysine, alanine can be present in a mole fraction of about 0.005 to about 0.600, glutamic acid can be present in a mole fraction of about 0.005 to about 0.300, and

lysine can be present in a mole fraction of about 0.2 to about 0.7. The molecular weight is between about 2,000 and about 40,000 daltons, and preferably between about 3000 and about 12,000 daltons.

When the molecular weight marker contains alanine, tyrosine and lysine, alanine can be present in a mole fraction of about 0.3 to about 0.6, tyrosine can be present in a mole fraction of about 0.005 to about 0.250, and lysine can be present in a mole fraction of about 0.1 to about 0.5. The molecular weight is between about 2,000 and about 40,000 daltons, and preferably between about 3000 and about 12,000 daltons.

When the molecular weight marker contains glutamic acid, tyrosine and lysine, glutamic acid can be present in a mole fraction of about 0.005 to about 0.300, tyrosine can be present in a mole fraction of about 0.005 to about 0.250, and lysine can be present in a mole fraction of about 0.3 to about 0.7. The molecular weight is between about 2,000 and about 40,000 daltons, and preferably between about 3000 and about 12,000 daltons.

Polypeptides of the invention can be used for molecular weight range determinations of other copolymers contemplated by the invention. Contemplated copolymers can consist of combinations of three, four, or five or more amino acids. In general, in order to determine the molecular weight range of a copolymer contemplated by the invention, the polypeptide molecular weight marker will have a defined molecular weight and an amino acid composition corresponding approximately to that of the copolymer. It will be apparent to one of skill in the art that any bias in the distribution of amino acids in a copolymer can be determined as described above for GLAT copolymer. For example, the relative amounts of amino acids incorporated at each position of a terpolymer population can be obtained by analyzing the products of each step of an Edman degradation. Alternatively, the proportions of amino acids incorporated into a terpolymer population during synthesis can be monitored. Where applicable, molecular weight markers can then be synthesized which reflect the bias. In addition, certain preferred terpolymer molecular weight markers will have alanine or tyrosine at position four.

Examples of preferred polypeptide molecular weight marker sequences are given in Table 1 (SEQ ID NOS: 1–7) using the conventional single letter amino acid code and reading from N-terminal to C-terminal. The seven indicated sequences are individual preparations of polypeptides having an amino acid composition corresponding to glatiramer acetate. Usually, amino acids comprising a molecular weight marker molecule are predominantly of one configuration (D- or L-configuration). In preferred embodiments, a molecular weight marker molecule is composed entirely of amino acids of the same configuration. However, molecular weight marker molecules comprising amino acids of mixed configuration may be preferred in certain embodiments where molecular weight is being determined for a glatiramer acetate preparation comprising amino acids of mixed configuration.

TABLE 1

Selected TV-marker amino acid sequences

TV-##	SEQ ID NO	Sequence
TV-35	1	AKKYAKKEKAAKKAYKKEAKAKAAEAAAKEAAYEA
TV-45	2	AKKYAKKAKAEKAKKAYKAAEAKKAAKYEKAAAEKAAAKEAAYEA
TV-56	3	AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAEAKYKAEAAKAAAKEAAYEA
TV-66	4	AKKYAKKEKAYAKAKKAEAKAAKKAKAEAKKYAKAAKAEKKEYAAAEAKYKAEAAKAAAKEAAYEA
TV-77	5	AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYAAAEAKYKAEAAKAAAKEAAYEA
TV-86	6	AKKYAKKEKAYAKKAEKAAKKAEAKAYKAAEAKKKAKAEAKKYAKAAKAEKKEYAAAEAKYKAEAAKKAYKAEAAKAAAKEAAYEA
TV-109	7	AKKYAKKAEKAYAKKAKAAKEKKAYAKKEAKAYKAAEAKKKAKAEAKKYAKEAAKAKKEAYKAEAKKYAKAAKAEKKEYAAEAKKAEAAKAYKAEAAKAAAKEAAYEA

In another embodiment, the present invention provides a plurality of molecular weight markers for determining the molecular weight of glatiramer acetate or a terpolymer on a molecular weight sizing column. The plurality of molecular weight markers are polypeptides. The plurality of markers can be two to about ten or more. In a preferred embodiment, the plurality of markers is about seven. Each polypeptide has an identified molecular weight which is between about 2,000 daltons and about 40,000 daltons, and an amino acid composition which corresponds approximately to that of glatiramer acetate or a terpolymer.

When such a plurality of molecular weight markers are used as standards for determining the molecular weight of glatiramer acetate or a terpolymer, a relationship which is approximately linear exists between the retention time of the molecular weight markers on the chromatographic column and the log of the molecular weight. A plurality of markers is used which is sufficient to establish the approximately linear relationship, although more may be employed. FIG. 3 shows the approximately linear relationship between relative retention time and log molecular weight for TV-markers of the invention.

In another embodiment, an approximately linear relationship exists between the molar ellipticity of the molecular weight markers and the molecular weight of the markers. When determining the molecular weight of a glatiramer acetate preparation by molar ellipticity, a plurality of markers is used which is sufficient to establish the approximately linear relationship, although more may be employed. A molecular weight for the glatiramer acetate or terpolymer

preparation is then obtained based on the linear relationship. FIG. 2 shows the approximately linear relationship between molar ellipticity and molecular weight for TV-markers of the invention.

Pharmaceutical Compositions Contemplated by the Invention—Molecular weight markers of the invention which correspond in composition to GLAT copolymer optimally have biological activity, and can be used for treatment of disease in the manner of GLAT copolymer. TV-markers having biological activity are alternately referred to as therapeutic markers. For example, GLAT copolymer is useful for the treatment of MS in humans as well as for blocking experimental allergic encephalomyelitis (EAE) in mice. Polypeptides of the invention having identified molecular weights and amino acid compositions corresponding to GLAT copolymer are shown herein to be active in the mouse model as well and demonstrate immunological characteristics which are similar to those of GLAT copolymer. Monoclonal antibodies which bind to GLAT copolymer also bind to TV-markers. Additionally, certain T cells which are stimulated by GLAT copolymer are also stimulated by molecular weight markers of the invention.

Similarly, a polypeptide having a defined molecular weight and corresponding in amino acid composition to a terpolymer having therapeutic utility will optimally have therapeutic utility. In general, polypeptide molecular weight markers corresponding in composition to a biologically active copolymer will optimally have similar biological activity.

The present molecular weight markers can be formulated into pharmaceutical compositions containing a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, sweeteners and the like. The pharmaceutically acceptable carriers may be prepared from a wide range of materials including, but not limited to, flavoring agents, sweetening agents and miscellaneous materials such as buffers and absorbents that may be needed in order to prepare a particular therapeutic composition. The use of such media and agents with pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The present compositions may be formulated as an injectable solution or suspension, a spray solution or a suspension.

Pharmaceutical compositions comprise an amount of one or more molecular weight markers of the invention. Preferably, the molecular weight markers consist essentially of three or all four of the amino acids tyrosine, alanine, glutamic acid and lysine in defined molar fractions. The molar fractions of the amino acids will be as set forth above.

In one embodiment, the molecular weight markers of the pharmaceutical composition are capable of binding to an MHC class II protein which, preferably, is associated with an autoimmune disease. The Class II MHC protein consists of approximately equal-sized α and β subunits, both of which are transmembrane proteins. A peptide-binding cleft is formed by parts of the amino termini of both α and β subunits. This peptide-binding cleft is the site of presentation of the antigen to T cells. There are at least three types of Class II MHC molecules: HLA-DR, HLA-DQ, and HLA-DP molecules. There are also numerous alleles encoding each type of these HLA molecules. The Class II MHC molecules are expressed predominantly on the surfaces of B lymphocytes and antigen presenting cells such as macrophages. Any available method can be used to ascertain whether the molecular weight marker binds to one or more MHC class II proteins. For example, the polypeptide can be radiolabeled or biotinylated, mixed with a crude or pure preparation of MHC class II protein and binding detected by adherence of the reporter molecule to the MHC class II protein after removal of the unbound polypeptide.

In another embodiment, the molecular weight markers are capable of binding to an MHC class II protein associated with multiple sclerosis. A polypeptide of this embodiment can have similar or greater affinity for the antigen binding groove of an MHC class II protein associated with multiple sclerosis than does Copolymer 1. Hence, the contemplated polypeptide can inhibit binding of or displace the binding of myelin autoantigens from the MHC class II protein. One MHC class II protein associated with multiple sclerosis is HLA-DR4 (DRB1*1501).

In another embodiment, molecular weight markers of the invention are capable of binding to an MHC class II protein associated with an arthritic condition, for example, rheumatoid arthritis or osteoarthritis. Accordingly, a polypeptide of this embodiment can have a greater affinity for the antigen binding groove of an MHC class II protein associated with the autoimmune disease than does a type II collagen 261–273 peptide. Hence, the contemplated polypeptide can inhibit binding of, or displace the type II collagen 261–273 peptide from the antigen binding groove of an MHC class II protein.

Therapeutic Methods Contemplated by the Invention—The present invention further provides methods for treating and preventing immune diseases in a mammal which include administering a therapeutically effective amount of a composition comprising a molecular weight marker of the invention.

Autoimmune diseases contemplated by the present invention include either cell-mediated disease (e.g. T cell) or antibody-mediated (e.g. B cell) disorders. Such disorders can be, inter alia, arthritic conditions, demyelinating diseases and inflammatory diseases. For example, autoimmune diseases which can be treated by the present polypeptides include multiple sclerosis (MS), rheumatoid arthritis (RA), osteoarthritis, autoimmune hemolytic anemia, autoimmune oophoritis, autoimmune thyroiditis, autoimmune uveoretinitis, Crohn's disease, chronic immune thrombocytopenic purpura, colitis, contact sensitivity disease, diabetes mellitus, Graves disease, Guillain-Barre's syndrome, Hashimoto's disease, idiopathic myxedema, myasthenia gravis, psoriasis, pemphigus vulgaris, or systemic lupus erythematosus. The present compositions can be used to treat one or more of these diseases.

The term "arthritic condition" as used herein is a condition wherein at least one symptom of rheumatoid arthritis is observed in at least one joint of a mammal, for example in a shoulder, knee, hip, backbone or a digit of the mammal. Examples of arthritic conditions include "polyarthritis", which is an arthritic condition that affects more than a single joint; "juvenile arthritis", an arthritic condition of humans under the age of 21; and Felty's syndrome, which can include the symptoms of neutropenia, splenomegaly, weight loss, anemia, lymphadenopathy, and pigment spots on the skin.

Immune-mediated diseases contemplated by the present invention are characterized by undesirable immune hypersensitivity to one or more antigens and include host-versus-

graft disease (HVGD) and graft-versus-host disease (GVHD), which are exemplified, respectively, by graft rejection by the host immune system and by attack on the host by donor T cells. These diseases are a significant barrier to transplantation systems such as organ transplantations and bone marrow reconstitutions. Other contemplated immune mediated diseases include delayed-type hypersensitivity (DTH) which is associated with contact antigens such as poison ivy and poison oak and various chemicals, as well as tuberculosis, leprosy, leishmaniasis, deep fungal infections, etc.

In one embodiment, any autoimmune disease can be treated by the present molecular weight markers so long as the contemplated marker binds to an MHC class II protein that has been associated with the autoimmune disease. One aspect of this embodiment provides a method which includes selecting a molecular weight marker that inhibits binding of an antigenic peptide to an MHC class II protein, for example, a method which further comprises selecting the molecular weight marker that inhibits class II-specific T cell responses to an MHC class II protein-peptide complex, and a method wherein the antigenic peptide is associated with an autoimmune disease; in another embodiment of the invention, a method is provided wherein the MHC class II protein is associated with an autoimmune disease.

In another embodiment, the method for treating an autoimmune disease in a mammal further involves inhibiting the proliferation or function of T cells which are responsive to an autoantigen. RA is a T cell-mediated autoimmune disease which can be treated with the present polypeptides. The pathological process of autoimmune diseases and immune rejection is mediated by T cells. Upon binding to and recognition of an antigen, T cells proliferate, secrete cytokines and recruit additional inflammatory and cytotoxic cells to the site. The present molecular weight markers prevent T cell proliferation and T cell functions such as cytokine secretion and recruitment of inflammatory and cytotoxic cells to the site. When the autoimmune disease is an arthritic condition the autoantigen can be collagen, and the present molecular weight markers can inhibit the proliferation and function of collagen-responsive T cells.

In another embodiment, the method for treating an autoimmune disease in a mammal involves binding the molecular weight marker to an antigen presenting cell such as a macrophage, a dendritic cell of the lymphoid tissue or an epidermal cell. The proliferation and functions of a T cell are activated when an appropriate antigen is presented to it. By binding to antigen presenting cells, the present molecular weight markers may block or otherwise interfere with T cell activation.

In yet another embodiment, the method for treating an autoimmune disease in a mammal involves binding the molecular weight marker to a major histocompatibility complex class II protein which is associated with an autoimmune disease. The Class II MHC proteins are expressed predominantly on the surfaces of B lymphocytes and antigen presenting cells such as macrophages. These Class II MHC proteins have a peptide-binding cleft which is the site at which antigenic peptides are presented to T cells. When the present polypeptides bind to a major histocompatibility complex class II protein, those polypeptides can block or otherwise interfere with antigen presentation and/or T cell activation.

In another embodiment, the method for treating an autoimmune disease in a mammal involves binding the molecular weight marker to Copolymer 1-reactive B cell antibodies, and/or Copolymer 1-reactive T cells. Copolymer 1-reactive T_H3 T cells facilitate the therapeutic effects of Copolymer 1. When binding to Copolymer 1-reactive T cells, the present molecular weight markers stimulate those T cells proliferate, secrete antiinflammatory cytokines and enhance the therapeutic benefits of treatment by the present methods. According to the present invention, the present molecular weight markers also bind to autoantigen-reactive antibodies which may block the antibody from attacking the target tissue, thereby helping to prevent the autoimmune disease from progressing.

The present molecular weight markers may be administered by any convenient route. In one embodiment the present molecular weight markers can be administered by injection to facilitate delivery to the tissues affected by the autoimmune disease. Thus, the present molecular weight markers may, for example, be injected, ingested, inhaled, or topically applied. The subject molecular weight markers may be incorporated into a cream, solution or suspension for topical administration. The present molecular weight markers are preferably administered orally, topically or by injection without addition of an adjuvant.

Useful Kits of the Invention—In an embodiment of the invention, a kit is provided for assaying the binding of an analyte to an MHC protein, which includes a water-soluble MHC protein, for example which has been recombinantly produced in a non-mammalian cell, and a means for detection of the bound analyte on the MHC protein, and instructions for use. The MHC protein used in the kit is an MHC class II protein selected from the group consisting of an MHC class II HLA-DR1 protein, an MHC class II HLA-DR2 protein and an MHC class II HLA-DR4 protein. The kit can further comprise an autoantigenic peptide. A kit of the invention can be used, for example, to test binding of a molecular weight marker of the invention to an MHC class II or inhibition of MHC binding of an autoantigenic peptide.

In a preferred embodiment, the MHC class II protein is produced in an invertebrate or a microbial cell, such as an insect cell or a yeast cell and is therefore devoid of bound peptide in the antigen cleft. The means for detecting binding of the analyte to the MHC protein can be any radioactive, fluorimetric, chemiluminescent, enzymatic or colorimetric means known to one of ordinary skill in the art. In a preferred embodiment, the MHC protein is a class II HLA-DR1 or HLA-DR4 protein. Examples of preferred autoantigenic peptide to be included are a collagen II peptide, a peptide derived from myelin basic protein, myelin oligodendrite protein, or a peptide from another protein implicated in an autoimmune disease.

The examples which follow describe the invention in detail with respect to showing how certain specific representative embodiments thereof can be made, the materials, apparatus and process steps being understood as examples that are intended to be illustrative only. In particular, the invention is not intended to be limited to the methods, materials, conditions, process parameters, apparatus and the like specifically recited herein.

Throughout this application, various publications, patents, and patent applications have been referred to. The teachings and disclosures of these publications, patents, and patent applications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which the present invention pertains.

It is to be understood and expected that variations in the principles of invention herein disclosed may be made by one skilled in the art and it is intended that such modifications are to be included within the scope of the present invention.

The following examples further illustrate the invention.

EXAMPLE 1

Physical Properties of TV-markers

Solid Phase Synthesis

Seven molecular weight markers were made with molecular weights ranging from about 3700–12000 daltons in the laboratory of Prof. M. Fridkin (Weizmann Institute of Science) (Table 2). These markers are referred to as TV-markers. The individual peptides were assigned a name TV-##, where ## is the number of amino acid residues (e.g. TV-35 is the 35-mer marker). The amino acid composition of these markers meets glatiramer acetate specifications (Table 2).

TABLE 2

	Ala	Glu	Tyr	Lys
TV-35 - Peptide with a molecular weight = 3757 daltons				
Number of residues	15	5	3	12
Molar fraction	0.429	0.143	0.086	0.343
TV-45 - Peptide with molecular weight = 4790 daltons				
Number of residues	20	6	4	15
Molar fraction	0.444	0.133	0.089	0.333
TV-56 - Peptide with a molecular weight = 6008 daltons				
Number of residues	24	8	5	19
Molar fraction	0.429	0.143	0.089	0.339
TV-66 - Peptide with a molecular weight = 7040 daltons				
Number of residues	29	9	6	22
Molar fraction	0.439	0.136	0.091	0.333
TV-77 - Peptide with a molecular weight = 8259 daltons				
Number of residues	33	11	7	26
Molar fraction	0.429	0.143	0.091	0.338
TV-86 - Peptide with a molecular weight = 9220 daltons				
Number of residues	37	12	8	29
Molar fraction	0.430	0.140	0.093	0.337
TV-109 - Peptide with a molecular weight = 11727 daltons				
Number of residues	46	15	10	38
Molar fraction	0.422	0.138	0.092	0.349

FIGS. 1*a*-1, 1*a*-2, 1*a*-3, 1*b*-1, 1*b*-2, 1*b*-3, 1c-1, 1c-2, 1c-3, 1*d*-1, 1*d*-2 and 1*d*-3 provide the distribution of alanine, lysine, glutamic acid and tyrosine, respectively, in the TV-markers described in Table 2. The amino acid position is defined by the X-axis, with the first amino acid corresponding to the C-terminal position. The presence of an amino acid is indicated by a vertical bar at the indicated amino acid position.

Confirmation of Mass and Sequence

Mass Spectroscopy—Polypeptide samples were analyzed immediately after their synthesis using a VG platform mass spectrophotometer equipped with an electronspray ion source. Several months later the analysis was repeated at TEVA using a PE-Sciex API300 mass spectrophotometer equipped with an electronspray ion source (Table 3, first preparation). These results indicate that each polypeptide TV-marker has a single, main component with the intended molecular mass.

TABLE 3

Mass Spectroscopy of Sequence-Defined Polypeptides

Polypeptide	Designed molecular mass (daltons)	Determined molecular mass - first preparation (daltons)	Determined molecular mass - second preparation (daltons)
TV-35	3757	3757	3757
TV-45	4790	4790	4790
TV-56	6008	6008	6008
TV-66	7040	7041	7040
TV-77	8259	8259	8259
TV-86	9220	9220	9220
TV-109*	11727	11728	11727

*The 109-mer was further purified by fractionation on a reversed-phase column. Three fractions were collected and fraction number 2 was designated for calibration purposes and referred to as TV-109.

A second batch of markers was prepared. Mass spectroscopy confirmed that the polypeptides of the second preparation were identical to the polypeptides of the first preparation (Table 3, second preparation). The similarity between the two preparations was also confirmed by chromatography on Superose 12. Each of the markers eluted with a sharp peak at a distinct retention time, regardless of the batch analyzed. Hence, the TV-markers of the present invention can be synthesized with reproducible mass.

Edman Degradation—The intended sequence of the polypeptides was confirmed by Edman degradation analysis of the first preparation.

Characterization of the Polypeptides

Circular Dichroism—Structural similarity between the molecular weight markers and glatiramer acetate is a prerequisite for an appropriate calibration of a molecular sizing column. Differences in polypeptide structure may result in different hydrodynamic size and consequently in altered retention time in the chromatographic system. The ellipticity, determined by circular dichroism, serves as a measure of the secondary structure of a polypeptide. When the ellipticity of the molecular weight markers and glatiramer acetate is similar, the structures of the two will be similar.

The molar ellipticity of the polypeptides was determined on a Jobin-Yvon CD spectrophotometer. FIG. 2 and Table 4 show that the extent of molar ellipticity correlated with the molecular weight of the polypeptide. The shortest peptide exhibited the lowest ellipticity value. The molar ellipticity of the new markers was of the same order of magnitude as those of the currently used glatiramer acetate molecular weight markers. Note that while the exact molecular weight for the TV-markers was plotted, the average-by-number molecular weight for the glatiramer acetate was used in the plot.

Thus, the new markers and glatiramer acetate possess similar structures and are therefore suitable for use as molecular weight markers for new preparations of glatiramer acetate.

TABLE 4

MW marker	MW (daltons)	Molecular Ellipticity M-ellip. (210 nm)
TV-markers		
TV-35	3757	-1.5367
TV-45	4790	-2.1651
TV-56	6008	-3.9658
TV-66	7040	-3.5172
TV-77	8259	-4.8365
TV-86	9220	-5.4546
TV-109	11727	-6.818
glatiramer acetate		
BD 743	3700	-2.0186
BD 714	5600	-4.4182
BD 681	6600	-5.2019
BD 677	7000	-6.0153
56895	8000	-6.9062
90995	8500	-9.1736
BD 656	8900	-8.8576

These analytical data indicate that the synthesized TV-marker polypeptides exhibit a substantial degree of similarity to the currently used glatiramer acetate molecular weight markers. The amino acid content is within glatiramer acetate specifications. The new polypeptides and the glatiramer acetate molecular weight markers have similar secondary structure, expressed as molar ellipticity. Consequently, TV-markers are expected to migrate or elute in a gel permeation chromatographic (GPC) system, such as Superose 12, like a glatiramer acetate preparation.

EXAMPLE 2

Superose 12 Column Calibration with TV-markers

TV-markers and a glatiramer acetate preparation are expected to demonstrate a similar correlation between relative retention time (RRT) and log molecular weight. The TV-markers were chromatographed on several Superose 12 columns. The peak retention time for each of the polypeptides was recorded. The linear correlation between Log Molecular Weight (MW) and the Relative Retention Time (RRT) was calculated as follows: RRT=B1+B2xLogMW (see FIG. 3*a* and Table 5).

The recently introduced Millennium-based data acquisition system (Waters Corp., Milford, Mass.) provides integrated calibration of GPC columns. The algorithm for the calibration is based on the retention time and is given by the equation:

$$LogMW=A+BxRT \text{ or } MW=10^{(A+BxRT)}$$

where MW is the molecular weight, RT is the retention time, A and B, respectively, are the intercept and the slope of the calculated regression function (FIG. 3*b*, Table 5).

The results obtained by this algorithm are practically identical to those obtained with the currently applied algorithm, based on RRT. In the effort to automate procedures, the Millennium-based data acquisition system was employed to perform the calibration using the TV-markers. The analytical methods were updated accordingly.

A good correlation (r^2>0.98) was obtained between log MW and RRT, although the points do not distribute evenly around the regression line. This distribution is due to the differences in the ellipticity of the various markers, as is also observed for the glatiramer acetate. The somewhat deviant-from-linearity low molecular weight marker cannot be excluded because the regression must cover values down to 2500 daltons for the first standard deviation (+1SD) distribution parameter. This is a general trait of all shorter peptides—they are less helical and more linear.

For the calibration based on the glatiramer acetate molecular weight markers, the intercept (B1) and slope (B_2) were, respectively, 1.7415 and -0.2784. This compares favorably with the calibration values obtained with TV-markers (B1=1.6996; B2=−0.2705). The molecular weights obtained using the two calibration sets within the specification range differed by, typically, not more than 20% in the low molecular weight range and by not more than 12% in the RRT specification range of the peak (average molecular weight). This relatively small difference supports the claim that these markers can replace the currently used glatiramer acetate molecular weight markers without significant change in the reported molecular weight values.

TABLE 5a

Calibration by glatiramer acetate MW-markers

Marker	MW	LOG MW	PEAK RT	RRT *
TV-35	3757	3.575	28.97	0.728
TV-45	4790	3.68	27.96	0.703
TV-56	6008	3.779	27.12	0.682
TV-66	7040	3.848	26.32	0.662
TV-77	8259	3.917	25.56	0.643
TV-86	9220	3.965	24.93	0.627
TV-109	11727	4.069	23.57	0.593
INTERCEPT	** A	6.2516	*** B1	1.6996
SLOPE	B	-0.0918	B2	-0.2705
r^2		0.9927		0.9923

* RRT = RT/RTAcetone

** calculated according Millennium eq. ... log MW = A + B × RT

*** calculated according to equation ... $B_1 + B_2 \times \log MW$

Calibration based on TV-markers was compared to calibration based on glatiramer acetate molecular weight markers (Table 5b). The two calibrations were compared by calculating molecular weight values for each calibration set in the RRT range of 0.5 to 0.8. The TV-marker calibration set included a fraction of TV-109 which was purified by reversed phase chromatography prior to use for column calibration.

TABLE 5b

Column Calibration by TV-markers

RRT	RT* (min)	Glatir.Ac. (MW1) Daltons	TV (0.1) (MWm) Daltons	Difference (MWm - MW1) Daltons	%
0.5	19.89	28800	26700	-2100	-7.3%
0.51	20.28	26500	24500	-2000	-7.5%
0.52	20.68	24400	22600	-1800	-7.4%
0.53	21.08	22500	20700	-1800	-8.0%
0.54	21.48	20700	19100	-1600	-7.7%
0.55	21.87	19000	17500	-1500	-7.9%
0.56	22.27	17500	16100	-1400	-8.0%
0.57	22.67	16100	14800	-1300	-8.1%
0.58	23.07	14900	13600	-1300	-8.7%
0.59	23.46	13700	12500	-1200	-8.8%
0.6	23.86	12600	11500	-1100	-8.7%
0.61	24.26	11600	10600	-1000	-8.7%
0.62	24.66	10700	9700	-1000	-9.3%
0.63	25.06	9800	9000	-800	-8.2%
0.64	25.45	9000	8200	-800	-8.9%
0.65	25.85	8300	7600	-700	-8.4%

TABLE 5b-continued

Column Calibration by TV-markers

RRT	RT* (min)	Glatir.Ac. (MW1) Daltons	TV (0.1) (MWm) Daltons	Difference (MWm - MW1) Daltons	%
0.66	26.25	7700	7000	-700	-9.1
0.67	26.65	7100	6400	-700	-9.9
0.68	27.04	6600	6900	-600	-9.2%
0.69	27.44	6000	5400	-600	-10.0%
0.70	27.84	5500	5000	-500	-9.1%
0.71	28.24	5100	4600	-500	-9.8%
0.72	28.63	4700	4200	-500	-10.6%
0.73	29.03	4300	3900	-400	-9.3%
0.74	29.43	4000	3600	-400	-10.0%
0.75	29.83	3600	3300	-300	-8.3%
0.76	30.23	3400	3000	-400	-11.8%
0.77	30.62	3100	2800	-300	-9.7%
0.78	31.02	2800	2500	-300	-10.7%
0.79	31.42	2600	2300	-300	-11.5%
0.80	31.82	2400	2100	-300	-12.5%

Purity of TV Markers—Three of the markers (TV-66, TV-77 and TV-86) were further purified by reversed phase chromatography. Three fractions were obtained for each marker. The middle fraction containing the major portion of the peak was chromatographed on the Superose 12 system in comparison to the unfractionated markers (Table 6). TV markers were size chromatographed without purification (Regular) and after purification by reversed-phase chromatography (Purified). Peak retention times were determined and the differences were calculated. The peak retention time remained unaffected by the degree of purity. Therefore, the final product of the synthesis is useful for accurate calibration and extra purification is not required.

TABLE 6

Effect of Purification on Retention Time

TV-marker	Retention Time (RT) (min) Regular	Purified	Difference (%)
TV-66	26.200	26.233	-0.13%
TV-77	25.450	25.450	0.00%
TV-86	24.867	24.850	0.07%

Consistency in Reported Values (Cross-validation)—Six batches of glatiramer acetate, manufactured in 1993 and 1994, were reanalyzed by GPC calibrated with the TV-markers. Their average molecular weight and the molecular weight distribution was compared to the values reported at the time of their release. Table 7 shows a comparison of molecular weight data from the original certificate of analysis and molecular weight data obtained using a Superose 12 column calibrated with TV-markers. The differences in reported values are typically less than 10%.

TABLE 7

Comparison of Molecular Weight Determinations

Cop 1 preparation		MW Millennium	MW CoA	% difference
00193	average	10250	9900	-3.5%
	-1 SD	20950	19100	-9.7%
	+1 SD	51000	4800	-6.3%
00594	average	6700	6550	-2.3%
	-1 SD	15700	15100	-4.0%
	+1 SD	3600	3400	-5.9%
00993	average	9200	8600	-7.0%
	-1 SD	18500	17350	-6.9%
	+1 SD	4700	4400	-6.8%
04194	average	6100	6150	0.8%
	-1 SD	12600	12500	-0.8%
	+1 SD	3200	3200	0.0%
01793	average	8800	8300	-6.0%
	-1 SD	18100	17300	-4.6%
	+1 SD	5200	4750	-9.5%
05494	average	8100	8300	2.4%
	-1 SD	17800	17450	-2.0%
	+1 SD	4100	4100	0.0%

Stability of Markers in Solution—TV-markers were chromatographed four times over a period of 24 hours. All markers were kept as solutions at room temperature and were analyzed at 8 hour intervals. Table 8 shows the peak retention time measured for the TV-markers at each of the four time points. At a concentration of 0.1 mg/ml, the TV-markers were stable in solution for at least 24 hours at room temperature.

TABLE 8

Stability of TV-markers in solution at room temperature

	Peak Retention Time (min)				Average	RSD
TV-35	29.883	29.883	29.900	29.950	29.904	0.106%
TV-45	28.933	28.917	28.917	28.933	28.925	0.032%
TV-56	28.250	28.217	28.283	28.250	28.250	0.095%
TV-66	27.400	27.350	27.433	27.433	27.404	0.143%
TV-77	26.750	26.700	26.750	26.783	26.746	0.128%
TV-86	26.117	26.100	26.150	26.150	26.129	0.095%
TV-109Fr 11	24.783	24.850	24.883	24.850	24.842	0.169%

In addition, solutions of the markers were stored for up to 3½ months under various storage conditions (2–8° C., −10 to −20° C., with/without azide). TV-markers are stable for at least 3 months when stored as frozen solutions (Table 9). As a precaution it was decided to allow storage of frozen solutions for two months.

Lyophilized TV-markers are stable for at least two years according to accumulated stability data.

TABLE 9

Stability of TV-markers at −10° to −20° C.

Date of calibration:		22 May 1997	09 Jul. 1997	04 Sep. 1997
Interval (days)		—	48	105
Marker	MW	RT	RT	RT
TV-35	3757	28.867	28.867	28.967
TV-45	4790	27.833	27.917	27.950
TV-56	6008	27.076	27.133	27.100
TV-66	7040	26.233	26.317	26.300
TV-77	8259	25.467	25.617	25.550
TV-86	9220	24.883	25.017	24.950
TV-109	11727	23.500	23.650	23.583

Summary of Calibration Data—Overall, the TV-markers were analyzed 53 times in two laboratories. A summary of

the data is presented in FIG. 4 and Table 10. The differences observed among the individual runs (FIG. 4) reflect variations between columns rather than differences between the participating laboratories. This is indicated in FIG. 4 by the use of different symbols for some of the runs. Calibration constants in Table 10 were calcualted using the Millennium equation for data obtained for 53 calibration sets injected into 16 columns.

TABLE 10

Calibration constants obtained in Plantex and Abic Labs

		RT			RT		Mean −	Mean +
Marker	MW	Mean	SD	RSD %	Min	Max	SD	SD
TV-35	3757	29.69	0.463	1.6%	28.85	30.35	28.30	31.08
TV-45	4790	28.72	0.481	1.7%	27.88	29.40	27.28	30.16
TV-56	6008	27.99	0.520	1.9%	27.08	28.77	26.43	29.55
TV-66	7040	27.19	0.526	1.9%	26.26	27.96	25.61	28.77
TV-77	8259	26.49	0.550	2.1%	25.51	27.33	24.84	28.14
TV-86	9220	25.89	0.556	2.1%	24.89	26.72	24.22	27.56
TV-109	11727	24.56	0.557	2.3%	23.53	25.41	22.89	26.23
Intercept (A)		6.4706	0.1220	1.9%	6.2561	6.6500	6.1046	6.8366
Slope (B)		−0.0969	0.0032	−3.3%	−0.1014	−0.0919	−0.1064	−0.0873
r^2		0.9901	0.0022	0.2%	0.9868	0.9828	0.9835	0.9967

Molecular Weight Distribution of a Glatiramer Acetate Preparation—Molecular weight was determined for a batch of glatiramer acetate (BN 90995). Table 11 summarizes data obtained from 16 determinations on TV-marker-calibrated columns.

TABLE 11

Date	Average	SD	RSD %
RT of glatiramer acetate (BN 90995)			
Peak	26.208	0.434	1.66
−2 SD (2.5%)	19.865	0.528	2.66
−1 SD (16%)	22.578	0.477	2.11
+1 SD (84%)	28.934	0.324	1.12
RRT of glatiramer acetate (BN 90995)			
Peak	0.664	0.014	2.09
−2 SD (2.5%)	0.503	0.016	3.09
−1 SD (16%)	0.572	0.015	2.54
+1 SD (84%)	0.733	0.011	1.53
MW (Daltons) of glatiramer acetate (BN 90995)			
Peak	7459	146	1.95
−1 SD (16%)	16622	466	2.80
+1 SD (84%)	4089	77	1.89

The application of a molecular weight and sequence-defined set of markers for the calibration of the Superose 12 column has several advantages over the currently used glatiramer acetate molecular weight markers.

First, the use of solid phase synthesis assures consistency among the various preparations of each batch. Mass spectroscopy results (Table 3) confirmed the reproducibility of the synthesis. This consistency provides improved accuracy in molecular weight determinations.

Second, the current calibration is based on the determination of the RRT at 50% of the peak area for each of the glatiramer acetate molecular weight markers. The new markers elute as sharp peaks. Their use in calibration is more accurate than the calculated retention time at 50% of the area of a broad peak.

Third, the use of markers having molecular weights defined by predetermined sequence precludes any uncertainty which might accompany the use of markers whose molecular weight is determined by inexact measurement of physical properties.

Fourth, the calibration procedure facilitates normalization of columns for molecular weight determinations, regardless of minor changes between column lots, age or instrumentation.

EXAMPLE 3

Biological Activity of TV-markers

Reactivity of TV-markers with Monoclonal Antibodies to Cop 1.—Table 12 shows the binding of anti-Cop 1 monoclonal antibodies to TV-markers. TV-markers and reference Glat production batches were tested. Microtiter wells were coated with 2 μg/ml antigen. Values are counts per minute (cpm) of ^{125}I-goat anti-mouse IgG bound to the monoclonal antibodies. Antibody binding to each TV-marker is compared to antibody binding to Cop 1 reference standard.

TABLE 12

Reactivity of TV-markers and Cop 1 with mAbs in RIA

	Binding of mAb cpm (% Cop 1 binding)		
Coating Antigen	anti-Cop-1 (3-3-9)	anti-Cop-1 (3-1-45)	anti-Cop-1 (5-7-2)
PBS	1364	315	521
03494 (glatiramer acetate)	14860	20587	10513
55296 (glatiramer acetate)	13705 (91)	17189 (83)	8683 (82)
55396 (glatiramer acetate)	13458 (90)	17564 (85)	9142 (86)
TV-35 (TV-marker)	1176 (0)	343 (0)	657 (1)
TV-56 (TV-marker)	1614 (2)	1581 (6)	9584 (91)

TABLE 12-continued

Reactivity of TV-markers and Cop 1 with mAbs in RIA

Coating Antigen	Binding of mAb cpm (% Cop 1 binding) anti-Cop-1 (3-3-9)	anti-Cop-1 (3-1-45)	anti-Cop-1 (5-7-2)
TV-77 (TV-marker)	2265 (6)	2152 (9)	4259 (37)
TV-86 (TV-marker)	1625 (2)	1606 (6)	8140 (76)

Reactivity with Cop 1 Specific T cells.—T cells lines which can be stimulated with GLAT copolymer were used to test stimulatory activity of TV-markers in comparison to regular GLAT copolymer production batches (Table 13). As above, the activities of TV-markers were tested for in vitro. The proliferation of various mouse and human T cell lines was determined in response to peptides in culture. The cell lines included: BALB/c-Ts-Cop-1, a tempreature-sensitive line derived from BALB/c mice; L-22-1, a tempreature-sensitive clone derived from F_1 mice; SC-103 and SC-14. human Cop 1 specific T cell clones. Proliferation was determined by measuring ^{3}H-thymidine uptake by the T cell lines cultured with 10 μg of GLAT copolymer or TV-marker.

Glatiramer acetate batches were stimulatory. TV-markers were also found to stimulate two of the four T cell lines, although not as strongly. TV-markers are recognized by both mouse and human T cells specific to glatiramer acetate. This confirms that there is amino acid sequence similarity and T cell epitope similarity among glatiramer acetate and TV-markers.

TABLE 13

Reactivity of glatiramer acetate and TV-markers with glatiramer acetate specific T cell lines

Antigen	^{3}H-Thymidine incorporation cpm (% Cop 1) BALB/c-Ts-Cop-1	L-22-1	SC-103	SC-14
PBS	588	207	342	760
03494 (glatiramer acetate)	32643	16395	8709	3091
55296 (glatiramer acetate)	35820 (110)	17315 (106)	7148 (81)	2973 (95)
55396 (glatiramer acetate)	34281 (105)	17211 (105)	7019 (80)	3253 (107)
TV-35 (TV-marker)	9465 (28)	225 (0)	438 (0)	884 (0)
TV-56 (TV-marker)	19545 (59)	232 (0)	237 (0)	3495 (117)
TV-77 (TV-marker)	17367 (52)	300 (1)	327 (0)	2701 (83)
TV-86 (TV-marker)	14694 (44)	418 (1)	298 (0)	2284 (65)

Blocking of Experimental Allergic Encephalomyelitis—To test the physiological activity of TV-markers, protection from experimental allergic encephalomyelitis (EAE) was investigated in mice. Injection of Copolymer 1 in complete Freund's adjuvant together with the encephalitogen can block EAE essentially as described in Aharoni et al., 17 *EUR. J. IMMUNOL.* 23 (1993). Other researchers have observed that the therapeutic effect of Copolymer 1 in multiple sclerosis patients is also associated with the induction of T_H2 cells. Lahat et al., 244 *J. NEUROL.* 129 (1997). In this example, EAE is blocked by different polypeptides of the present invention.

Induction of EAE—Two to three month old female (SJL/JxBALB/c)F1 mice are injected in all four footpads with mouse spinal cord homogenate (3.5 mg/mouse) emulsified in a 1:1 ratio in complete Freund's adjuvant (CFA) supplemented with 4 mg/ml mycobacterium tuberculosis H37Ra. Pertussis toxin (0.25 ml, 250 ng, Sigma) is injected intravenously, immediately after and 48 hr later. Mice are examined daily from day 10 post induction for clinical signs of EAE which were scored on a 0–5 scale as described in Lando et al., 123 *J. IMMUNOL.* 2156 (1979).

EAE Blocking by Injection with Complete Adjuvant—Each antigen being tested was included in the encephalitogenic inoculum. Table 14 shows the incidence of EAE in animals which received the encephalitogenic inoculum supplemented with a TV-marker or glatiramer acetate and in animals which received only the encephalitogenic inoculum. Also shown is the mean onset of EAE in animals which were not protected. Disease intensity is scored daily in mice with a score of zero (0=healthy) to five (5=dead). The onset is determined as the day an animal exhibits a disease score of at least one (1).

TABLE 14

Protection from EAE by TV-markers

Blocking Antigen	Incidence	Mean Score	Mean Onset (days)	% Blocking
None (control)	10/10	4.9	11.3	—
TV-45	0/10	0	—	100
TV-66	6/10	2.8	11.7	40
TV-77	1/9	0.2	14.0	89
TV-86	3/10	0.7	12.0	70
TV-109	0/10	0	—	100
03494	0/10	0	—	100
55396	0/10	0	—	100

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        35                  40                  45

Ala Glu Lys Lys Glu Tyr Ala Ala Ala Glu Ala Lys Tyr Lys Ala Glu
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Tyr Ala Lys Glu Ala Ala Lys Ala Lys Lys Glu Ala Tyr Lys Ala Glu
    50                  55                  60

Ala Lys Lys Tyr Ala Lys Ala Ala Lys Ala Glu Lys Lys Glu Tyr Ala
65                  70                  75                  80

Ala Ala Glu Ala Lys Lys Ala Glu Ala Ala Lys Ala Tyr Lys Ala Glu
                85                  90                  95

Ala Ala Lys Ala Ala Ala Lys Glu Ala Ala Tyr Glu Ala
            100                 105
```

What is claimed:

1. A method of treating a human afflicted with multiple sclerosis comprising administering to the human a single purified polypeptide, wherein the purified polypeptide comprises consecutive amino acids the amino acid sequence of which is set forth in any of SEQ ID NO:2 or SEQ ID NO:7 in an amount effective to treat the human.

2. The method of claim 1 wherein the purified polypeptide consists entirely of L-amino acids.

3. The method of claim 1, wherein the amino acid sequence of the consecutive amino acids is set forth in SEQ ID NO: 2.

4. The method of claim 1, wherein the amino acid sequence of the consecutive amino acids is set forth in SEQ ID NO: 7.

5. A method of treating a human afflicted with multiple sclerosis comprising administering to the human a pharmaceutical composition comprising a single purified polypeptide, wherein the purified polypeptide comprises consecutive amino acids the amino acid sequence of which is set forth in any of SEQ ID NO:2 or SEQ ID NO:7, in an amount effective to treat the human and a pharmaceutically acceptable carrier.

6. A method of inhibiting the progression of multiple sclerosis in a human afflicted with multiple sclerosis comprising administering to the human a single purified polypeptide, wherein the purified polypeptide comprises consecutive amino acids the amino acid sequence of which is set forth in any of SEQ ID NO:2 or SEQ ID NO:7, in an amount effective to inhibit the progression of multiple sclerosis in the human.

7. The method of claim 6, wherein, the purified polypeptide consists entirely of L-amino acids.

8. The method of claim 6, wherein the amino acid sequence of the consecutive amino acids is set forth in SEQ ID NO: 2.

9. The method of claim 6, wherein the amino acid sequence of the consecutive amino acids is set forth in SEQ ID NO: 7.

10. A method of inhibiting the progression of multiple sclerosis in a human afflicted with multiple sclerosis comprising administering to the human a pharmaceutical composition comprising a single purified polypeptide, wherein the purified polypeptide comprises consecutive amino acids the amino acid sequence of which is set forth in any of SEQ ID NO:2 or SEQ ID NO:7, in an amount effective to inhibit the progression of multiple sclerosis in the human and a pharmaceutically acceptable carrier.

* * * * *

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(12) **United States Patent**
Konfino et al.

(10) **Patent No.: US 6,939,539 B2**
(45) **Date of Patent: Sep. 6, 2005**

(54) **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(52) **U.S. Cl.** **424/78.08**; 424/78.37; 424/78.17; 424/78.26; 424/78.29; 514/2; 514/12; 514/561; 514/903; 525/420; 525/434; 525/435; 528/328

(58) **Field of Search** 424/78.08, 78.17, 424/78.26, 78.29, 78.37, 514/2, 12, 561, 903; 525/420, 434, 435; 528/328

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(57) **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

33 Claims, 2 Drawing Sheets

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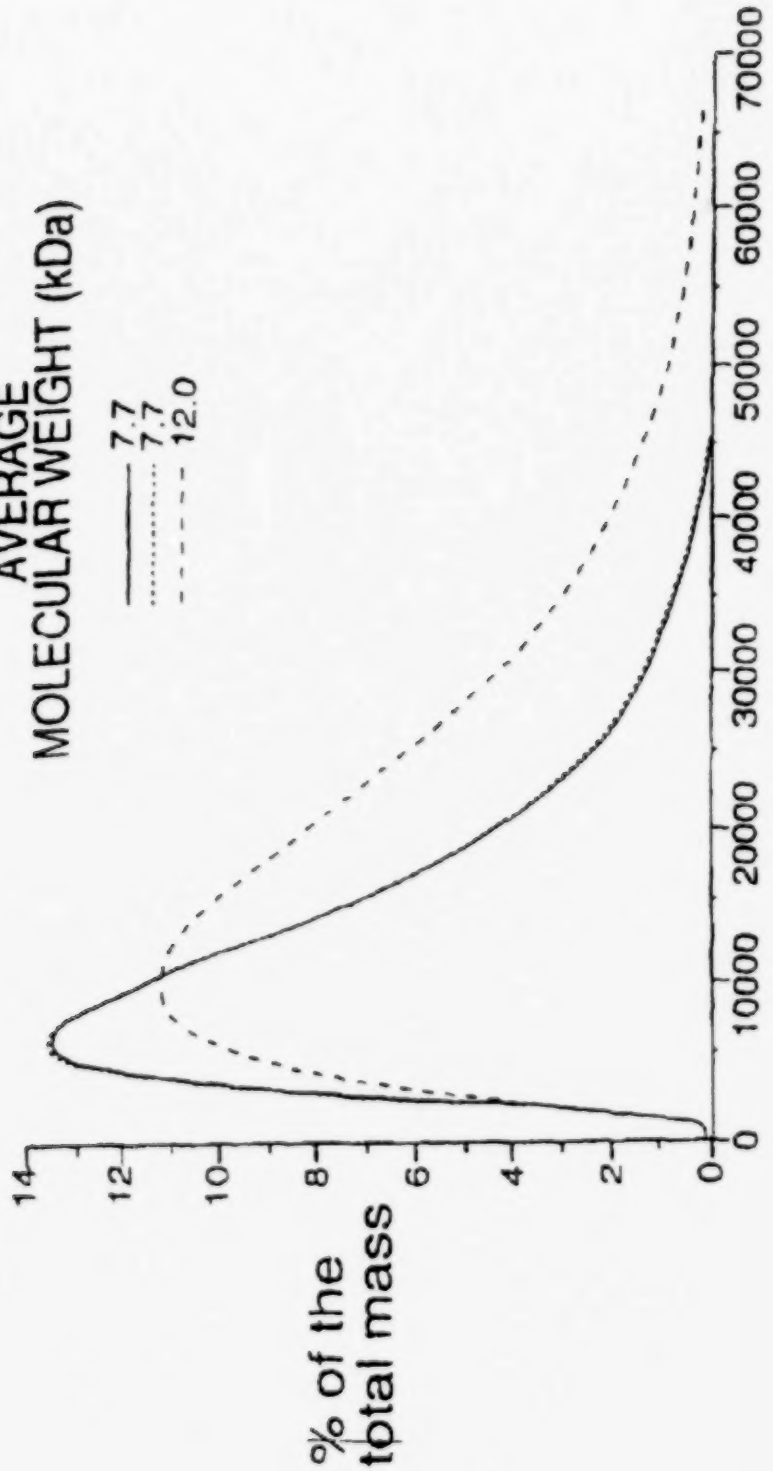

AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
% of the total mass
0
2
4
6
8
10
12
14
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 1

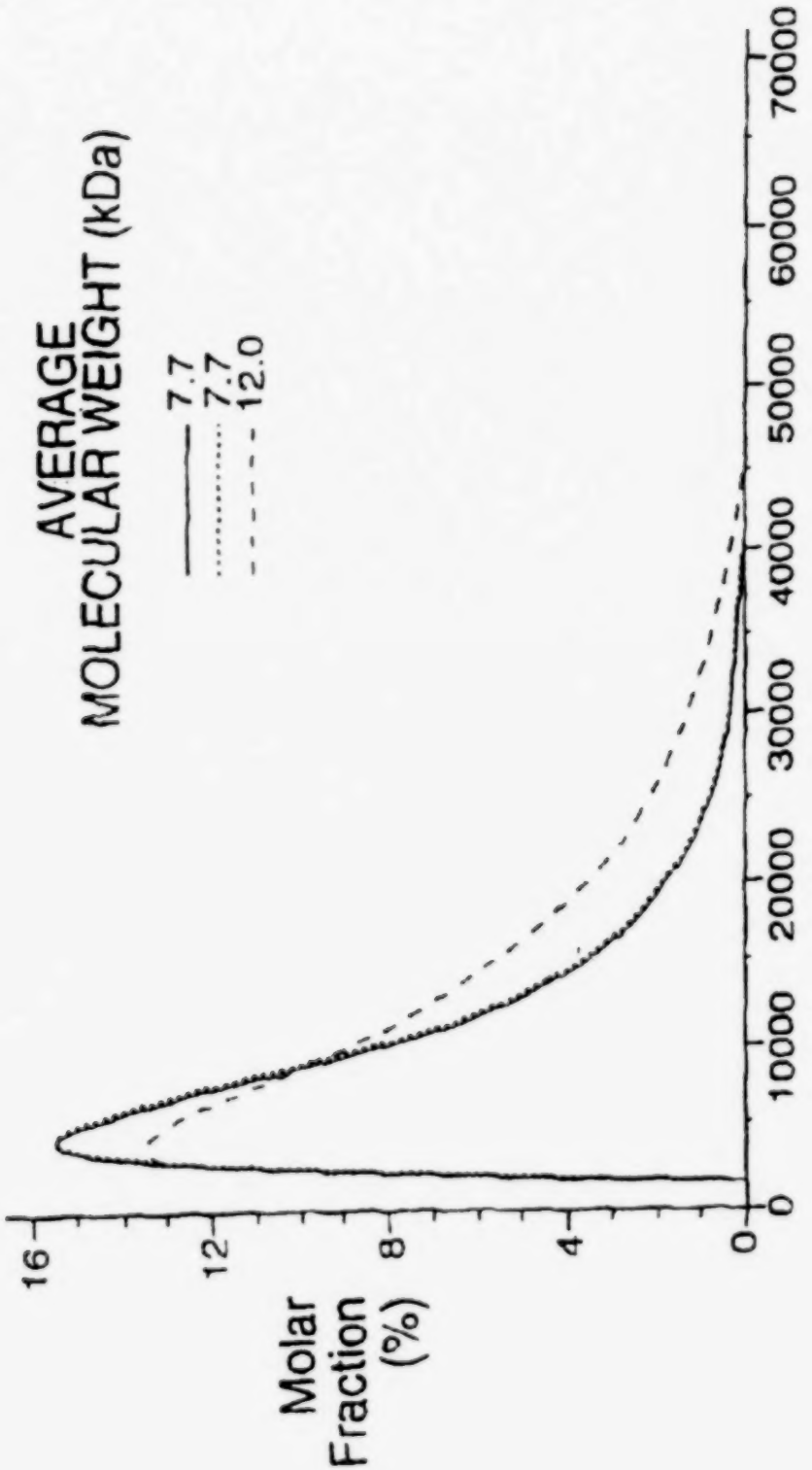

AVERAGE MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar Fraction (%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a continuation of application U.S. Ser. No. 10/014,477 filed Dec. 14, 2001 now U.S. Pat. No. 6,620,847, which is a continuation of application Ser. No. 09/510,466, filed Feb. 22, 2000, now U.S. Pat. No. 6,362,161, which is a continuation of U.S. Ser. No. 09/032,334 filed Feb. 27, 1998, now U.S. Pat. No. 6,048,898, which is a continuation of U.S. Ser. No. 08/447,146, filed May 22, 1995, now U.S. Pat. No. 5,800,808, which is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6.2:5.1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa.

FIG. 2 shows similar data relating to the molar fraction

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and ε-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic Method of Preparation of Low-Toxicity Copolymer-1

Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600x26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column

was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg/ml, in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an average molecular weight of 7-8 KDa was isolated between 120-130 minutes (Batch A).

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7-8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A: In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B: In Vitro

RBL—Degranulation Test

I. Introduction

Histamine (or serotonin) release from basophils is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-2H$_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (L. L. Basuman, C. Isersky, M. G. Petrino and R. P. Siraganian. Eur J. Immunol. 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among the , are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and or systemic side effects.

II. Principle of the Test Method

Rat Basophilic Leukemia cells (RBL-2H$_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250-14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table:

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,840	<2.5	21.0
13,000	>5	66.9
14,500	>5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20-28° C. a test reaction is performed on every batch at different time periods for example, from 10-50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of Low-toxicity Copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°-20° C. against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5-6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

What is claimed is:

1. A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence, and wherein the composition is suitable for treating multiple sclerosis.

2. The composition of claim 1, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

3. The composition of claim 1, wherein less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

4. The composition of claim 3, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

5. The composition of claim 4, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

6. The composition of claim 1, wherein the mixture has an average molecular weight of about 4 to about 8.6 kilodaltons.

7. The composition of claim 1, wherein the mixture has an average molecular weight of about 5 to about 9 kilodaltons.

8. The composition of claim 1, wherein less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

9. The composition of claim 8, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

10. The composition of claim 9, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

11. The composition of claim 1, wherein the mixture has a molecular weight distribution substantially as depicted in the curves of FIG. 1 or FIG. 2 in which the average molecular weight is about 7.7 kDa.

12. A pharmaceutical composition comprising:

a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition, wherein the copolymer-1 composition comprises a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence, and

a pharmaceutically acceptable excipient.

13. The pharmaceutical composition of claim 12, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

14. The pharmaceutical composition of claim 12, wherein less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

15. The pharmaceutical composition of claim 14, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

16. The pharmaceutical composition of claim 15, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

17. The pharmaceutical composition of claim 12, wherein the mixture has an average molecular weight of about 4 to about 8.6 kilodaltons.

18. The pharmaceutical composition of claim 12, wherein the mixture has an average molecular weight of about 5 to about 9 kilodaltons.

19. The pharmaceutical composition of claim 12, wherein less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

20. The pharmaceutical composition of claim 19, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

21. The pharmaceutical composition of claim 20, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

22. The pharmaceutical composition of claim 12, wherein the mixture has a molecular weight distribution substantially as depicted in the curves of FIG. 1 or FIG. 2 in which the average molecular weight is about 7.7 kDa.

23. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 12.

24. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 13.

25. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 14.

26. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 15.

27. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 16.

28. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 17.

29. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 18.

30. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 19.

31. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 20.

32. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 21.

33. A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 22.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,939,539 B2
DATED : September 6, 2005
INVENTOR(S) : Konfino et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

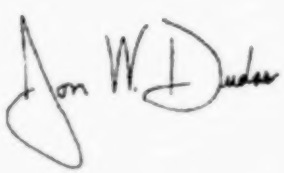
Title page,
Item [56]. **References Cited**, OTHER PUBLICATIONS, "D. Titelbaum et al." reference, change "Copolymre 1" to -- Copolymer 1 --.

Column 4,
Line 34, change "tritluoroacetyllysine" to -- trifluoroacetyllysine --.

Column 6,
Line 28, change "84 kilodaltons" to -- 8.4 kilodaltons --.

Signed and Sealed this

First Day of November, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

US007199098B2

(12) **United States Patent**
Konfino et al.

(10) **Patent No.: US 7,199,098 B2**
(45) **Date of Patent: *Apr. 3, 2007**

(54) **COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**

(75) Inventors: **Eliezer Konfino**, Ramat Gan (IL); **Michael Sela**, Rehovot (IL); **Dvora Teitelbaum**, Rehovot (IL); **Ruth Arnon**, Rehovot (IL)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/098,432**

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Related U.S. Application Data

(63) Continuation of application No. 10/615,865, filed on Jul. 10, 2003, now Pat. No. 6,939,539, which is a continuation of application No. 10/014,477, filed on Dec. 14, 2001, now Pat. No. 6,620,847, which is a continuation of application No. 09/510,466, filed on Feb. 22, 2000, now Pat. No. 6,362,161, which is a continuation of application No. 09/032,334, filed on Feb. 27, 1998, now Pat. No. 6,048,898, which is a continuation of application No. 08/447,146, filed on May 22, 1995, now Pat. No. 5,800,808, which is a continuation-in-part of application No. 08/344,248, filed on Nov. 23, 1994, now abandoned, which is a continuation of application No. 08/248,037, filed on May 24, 1994, now abandoned.

(51) **Int. Cl.**

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(58) **Field of Classification Search** 424/78.08, 424/78.37, 78.17, 78.26, 78.29; 514/561, 514/2

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

20 Claims, 2 Drawing Sheets

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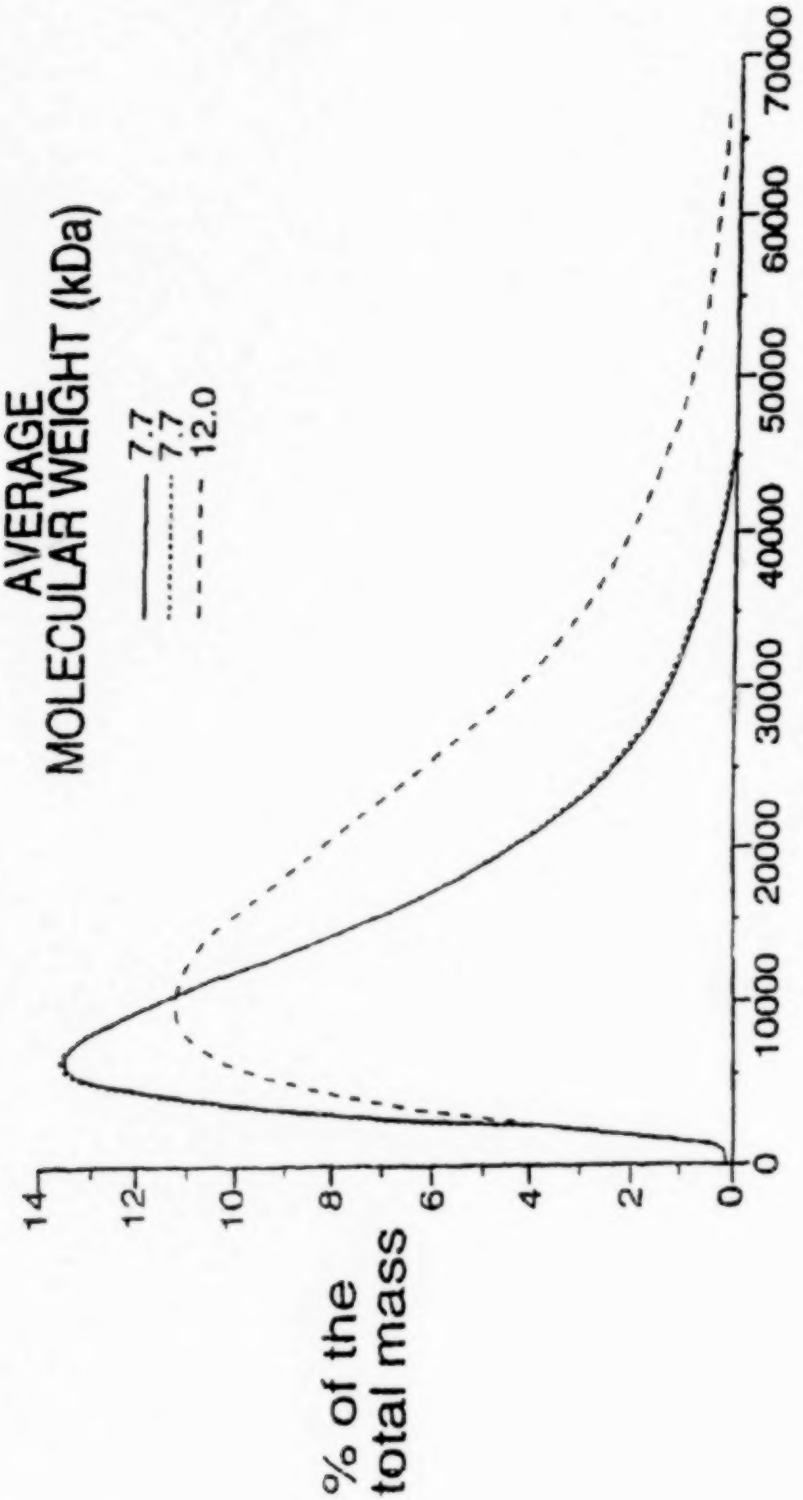
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
% of the
total mass
0
2
4
6
8
10
12
14
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 1

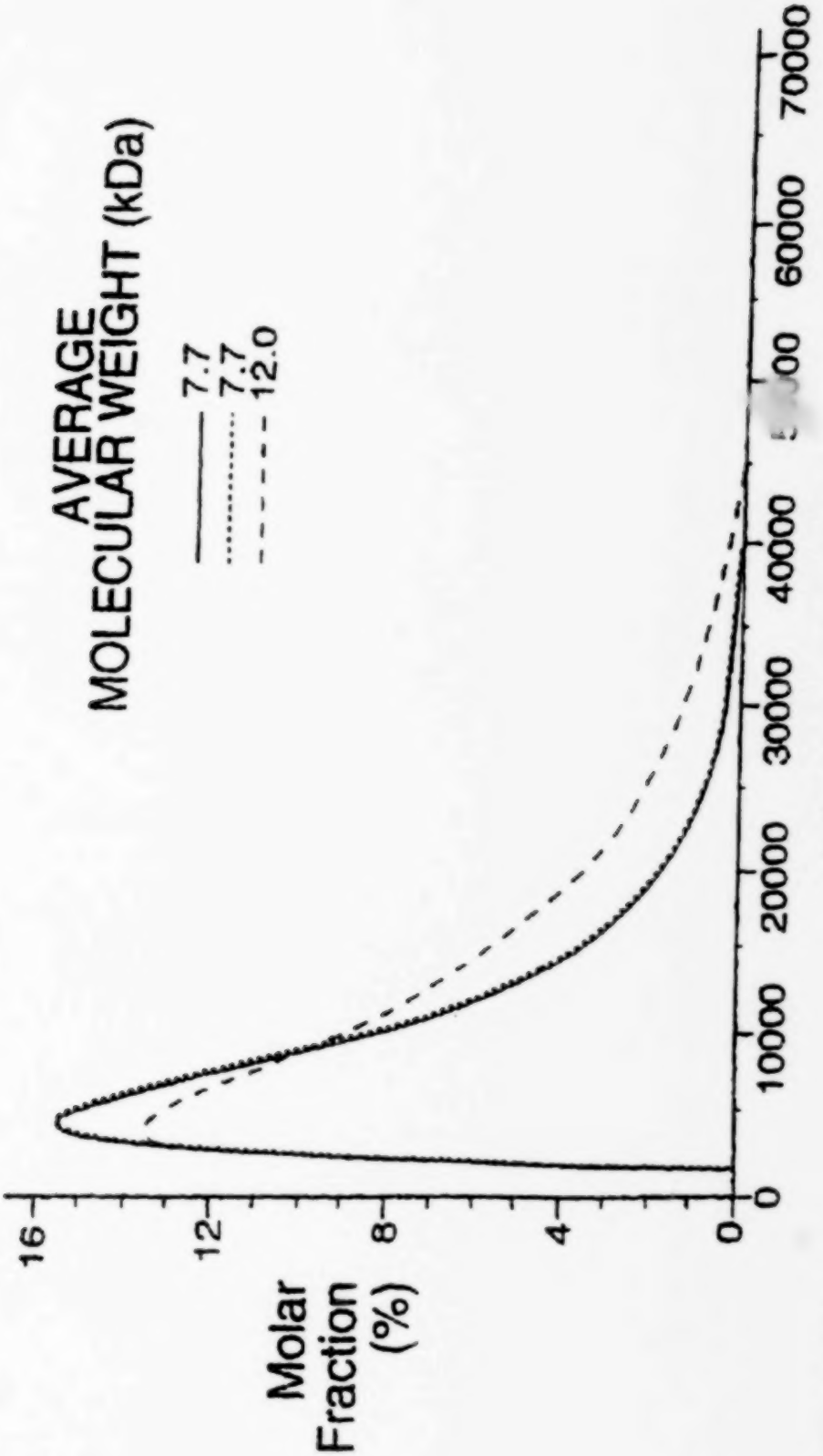
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
60000
70000
Molecular Weight

FIG. 2

COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a continuation application of U.S. Ser. No. 10/615,865, filed Jul. 10, 2003, now U.S. Pat. No. 6,939,539, which is a continuation of application U.S. Ser. No. 10/014,477, filed Dec. 14, 2001, now U.S. Pat. No. 6,620,847, which is a continuation of application Ser. No. 09/510,466, filed Feb. 22, 2000, now U.S. Pat. No. 6,362,161, which is a continuation of U.S. Ser. No. 09/032,334 filed Feb. 27, 1998, now U.S. Pat. No. 6,048,898, which is a continuation of U.S. Ser. No. 08/447,146, filed May 22, 1995, now U.S. Pat. No. 5,800,808, which is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6.2:5.1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species

with molecular weight above 40 KDa. FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and ε-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26° C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic method of preparation of low-toxicity copolymer-1. Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600x26 mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg/ml in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an average molecular weight of 7 8 KDa was isolated between 120 130 minutes (Batch A).

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7 8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A: In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic"

B: In Vitro

RBL Degranulation Test

I. Introduction

Histamine (or serotonin) release from basophile is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-$2H_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (E. T. Hasumian, C Isersky, M. G. Petrino and R. P. Siraganian. Eur. J. Immunol. 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation testis, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects.

II. Principle of the Test Method

Rat Basophilic Leukemia cells (RBL-$2H_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 μg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250 14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table

Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
6,250	<2.5	12.4
7,300	<2.5	21.0
13,000	>5	66.9
14,900	>5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01 0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6 12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ-benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01–0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20–28° C. a test reaction is performed on every batch at different time periods for example, from 10–50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular-weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of Low-toxicity Copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°–20° C. against water until a pH 8 is attained. It is then dialyzed against an 0.3% acetic acid and again water until a pH 5.5–6.0 is attained. This solution is then concentrated and lyophilized to dryness.

The invention claimed is:

1. A copolymer-1 composition comprising a mixture of copolymers of alanine, glutamic acid, lysine and tyrosine, the copolymer species in the mixture being non-uniform with respect to molecular weight and sequence, wherein over 75% of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of 2 kDa to 20 kDa and less than 5% of the copolymers have a molecular weight above 40 kDa, and wherein the composition is suitable for treating multiple sclerosis.

2. The composition of claim **1**, wherein the mixture has an average molecular weight of 7000 Da±2000 Da.

3. The composition of claim **1**, wherein the mixture has an average molecular weight of 4 to 8.6 kDa.

4. The composition of claim **1**, wherein the mixture has an average molecular weight of 6.25 to 8.4 kDa.

5. The composition of claim **1**, wherein the mixture has an average molecular weight of 4 to 8 kDa.

6. The composition of claim **1**, wherein the mixture has an average molecular weight of 7 to 8 kDa.

7. The composition of claim **1**, wherein the mixture has a molecular weight distribution as depicted in FIG. **1** for the mixture with an average molecular weight of 7.7 kDa.

8. The composition of claim **1**, wherein less than 2.5% of the copolymers in the mixture have a molecular weight above 40 kDa.

9. The composition of claim **8**, wherein the mixture has an average molecular weight of 7000 Da±2000 Da.

10. The composition of claim **8**, wherein the mixture has an average molecular weight of 4 to 8.6 kDa.

11. The composition of claim **8**, wherein the mixture has an average molecular weight of 6.2 5 to 8.4 kDa.

12. The composition of claim **8**, wherein the mixture has an average molecular weight of 4 to 8 kDa.

13. The composition of claim **8**, wherein the mixture has an average molecular weight of 7 to 8 kDa.

14. The composition of claim **8**, wherein the mixture has a molecular weight distribution as depicted in FIG. **1** for the mixture with an average molecular weight of 7.7 kDa.

15. A process for preparing a copolymer-1 composition having an average molecular weight of 4 to about 8.6 kDa comprising:

polymerizing a mixture of an N-carboxyanhydride of tyrosine, an N-carboxyanhydride of alanine, γ-benzyl glutamate and trifluoroacetyllysine in a molar ratio of 1:5:2:4 to form a mixture of protected polypeptides;

deprotecting the protected polypeptides to form a mixture of unprotected polypeptides; and

isolating a copolymer-1 composition of unprotected polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the copolymer-1 composition has an average molecular weight of 4 to 9 kDa.

16. The process of claim **15**, wherein the copolymer-1 composition has an average molecular weight of 6.25 to 8.4 kilodaltons.

17. A copolymer-1 composition having an average molecular weight of about 4 to about 8.6 kDa preparable by a process comprising:

polymerizing a mixture of an N-carboxyanhydride of tyrosine, an N-carboxyanhydride of alanine, γ-benzyl glutamate and trifluoroacetyllysine in a molar ratio of 1:5:2:4 to form a mixture of protected polypeptides;

deprotecting the protected polypeptides to form a mixture of unprotected polypeptides; and

isolating a mixture of unprotected polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of 4 to 9 kDa.

18. The composition of claim **17**, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

19. A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of 4 to about 8.6 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence, and wherein the composition exhibits lower toxicity than a copolymer-1 composition having an average molecular weight greater than about 8.6 kilodaltons.

20. The composition of claim **19**, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,199,098 B2
APPLICATION NO. : 11/098432
DATED : April 3, 2007
INVENTOR(S) : Konfino et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below.

Claim 15, col. 6 line 31, change "4 to 9" to --4 to about 8.6--

Claim 17, col. 6 line 47, change "4 to 9" to --4 to about 8.6--

Signed and Sealed this

Twenty-ninth Day of September, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

March 18, 2009

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APPLICATION NUMBER: *10/615,865*
FILING DATE: *July 10, 2003*
PATENT NUMBER: *6939539*
ISSUE DATE: *September 06, 2005*

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
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* * *

Listing of Claims:

Claims 1-19 (Canceled).

20. (Currently amended) A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, ~~and~~ wherein the mixture of polypeptides is non-uniform with respect to molecular weight and ~~constitution~~ sequence, and wherein the composition is suitable for treating multiple sclerosis.

21. (Previously presented) The composition of claim 20, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

22. (Currently amended) The composition of claim 20, wherein less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

23. (Previously presented) The composition of claim 22, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

24. (Previously presented) The composition of claim 23, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

25. (Previously presented) The composition of claim 20, wherein the mixture has an average molecular weight of about 4 to about 8.6 kilodaltons.

26. (Previously presented) The composition of claim 20, wherein the mixture has an average molecular weight of about 5 to about 9 kilodaltons.

27. (Currently amended) The composition of claim 20, wherein less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

28. (Previously presented) The composition of claim 27, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

29. (Previously presented) The composition of claim 28, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

30. (Previously presented) The composition of claim 20, wherein the mixture has a molecular weight distribution substantially as depicted in the curves of Figure 1 or Figure 2 in which the average molecular weight is about 7.7 kDa.

31. (Canceled)

32. (Canceled)

33. (New) A pharmaceutical composition comprising:

a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition, wherein the copolymer-1 composition comprises a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence; and

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a pharmaceutically acceptable excipient.

34. (New) The pharmaceutical composition of claim 33, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

35. (New) The pharmaceutical composition of claim 33, wherein less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

36. (New) The pharmaceutical composition of claim 35, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

37. (New) The pharmaceutical composition of claim 36, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

38. (New) The pharmaceutical composition of claim 33, wherein the mixture has an average molecular weight of about 4 to about 8.6 kilodaltons.

39. (New) The pharmaceutical composition of claim 33, wherein the mixture has an average molecular weight of about 5 to about 9 kilodaltons.

40. (New) The pharmaceutical composition of claim 33, wherein less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

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41. (New) The pharmaceutical composition of claim 40, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

42. (New) The pharmaceutical composition of claim 41, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

43. (New) The pharmaceutical composition of claim 33, wherein the mixture has a molecular weight distribution substantially as depicted in the curves of Figure 1 or Figure 2 in which the average molecular weight is about 7.7 kDa.

44. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 33.

45. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 34.

46. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 35.

47. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 36.

48. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 37.

49. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 38.

50. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 39.

51. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 40.

52. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 41.

53. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 42.

54. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 43.

DEC 0 1 2004
PATENT & TRADEMARK OFFICE

PATENT
1662/466073

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	KONFINO et al.
APPLICATION SERIAL NO:		10/615,865
FILED	:	July 9, 2003
FOR	:	COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS
EXAMINER	:	Examiner F. Krass
GROUP ART UNIT	:	1614

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

In response to the office action dated June 1, 2004, Applicants respectfully request reconsideration in view of the following amendments and remarks. The fee for a three-month extension of time is enclosed. However, the Commissioner is hereby authorized to charge any payment due in connection with these papers, or credit any overpayment, to Deposit Account No. 11-0600.

12/02/2004 LWONDIM1 00000092 110600 10615865
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PATENT
Docket No. 1662/466073

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	KONFINO et al.
APPLICATION SERIAL NO:		10/615,865
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FOR	:	COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS
EXAMINER	:	Examiner F. Krass
GROUP ART UNIT	:	1614

Declaration of YAFIT STARK under 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Yafit Stark, Ph.D., currently residing at 22 Uziel Street, Givat Shmuel, Israel, hereby declare the following:

1. I am the Senior Director of the Global Clinical Research Corporate Innovative R & D Division, Teva Pharmaceuticals Ltd., the exclusive licensee of United States Patent Application No. 10/615,865, filed July 9, 2003, for which a patent is being sought in the present application. I have read and understood the present application, and I am highly familiar with Copaxone®, a preferred embodiment of the present invention, especially with respect to clinical studies involving this drug.

2. I received a Ph.D. degree from Tel Aviv University, Israel, in 1985. I have worked in the area of pharmaceutical research for Teva Pharmaceuticals since 1987. For the past 13 years, I have been personally responsible for the clinical development and research of Copaxone®. My *curriculum vitae* is attached.

TEV000304789

3. I have been asked to comment on some of the purposes of the following clinical trials: "Clinical Trial Protocol No. 9001; first patient enrolled October 23, 1991" and "Clinical Trial Protocol No. 9002; first patient enrolled June 17, 1993," hereinafter referred to as "9001" and "9002", respectively.

4. One purpose of clinical trial 9001 was to verify that an improvement in a copolymer-1 composition, reducing toxicity by lowering the average molecular weight, did not diminish or negate the effectiveness of the composition in treating multiple sclerosis.

5. One purpose of clinical trial 9002 was to collect and verify the long-term safety of the improved copolymer-1 composition.

6. Thus, clinical trials 9001 and 9002 were necessary to verify the efficacy and pharmaceutical viability of the claimed invention.

I, Yafit Stark, declare under penalty of perjury that the above statements are true and correct to the best of our knowledge, information, and belief. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Dated: 22 NOV 2004

Yafit Stark

CURRICULUM VITAE

Name:	Yafit Stark Ph.D.
Title:	Senior Director Global Clinical Research Corporate Innovative R & D Division, Teva Pharmaceuticals Ltd.
Home Address:	22 Uziel Street, Givat Shmuel, Israel.
Tel (home):	03-5323343
Date & Place of Birth:	24 June, 1953, Israel.
Military Service (Zahal):	1971 - 1973
Marital Status:	Married + 3 children

EDUCATION

1973 - 1976:	B.Sc.,Bar Ilan University, Physiology. Zoology.
1976 - 1979:	M.Sc., Tel Aviv University, Pathology. Under the direction of Prof. M. Wolman. "Study of the Combined Effect of Treatment with Levan and Cytotoxic Drugs on the Development and Cure of a Malignant Tumor in Mice".
1980 - 1985:	Ph.D., Tel Aviv University, Pathology. Under the direction of Prof. M. Wolman and Dr. J. Leibovici. "The Direct Effect of Levan on Tumor Cells: Conditions and Mechanisms".
1986 - 1987:	Post-doctoral fellowship - Tel Aviv University and the Weizman Institute, under the direction of Prof. B. Grifell. "Epithelial Cell Differentiation - Immuno-Histopathological Research".

Yafit Stark, Ph.D.

POSITIONS HELD:

From Aug. 1994: Senior Director Global Clinical Research, Clinical Trials Department, Innovative R & D, TEVA Pharmaceutical Industries, Ltd., P. O. Box 8077, Kiryat Nordau, Netanya, Israel.

Responsible for;

- planning and execution of the clinical development plan of all the company's innovative drugs.
- Planning and execution of bioequivalence studies for the company's generic products.
- Providing clinical supplies for clinical studies, including packaging, distribution, follow-up, destruction and drug accountability for all global studies.
- Management of Drug Safety according to the relevant laws and regulations
- Ensuring compliance of clinical studies with ICH-GCP Guidelines, and in accordance with laws applicable in the relevant countries and Teva's Standard Operating Procedures.

1991-1994 Director of R&D Clinical Research, TEVA USA
Responsible for planning and execution of clinical trials in the USA for Teva's innovative drug, Copaxone

1990-1991 Clinical Studies Manager, Innovative R&D, TEVA Pharmaceutical Industries, Ltd. Israel
Responsible for managing clinical trials with TEVA's innovative compounds

1987-1990 Project Manager. Innovative R&D, TEVA Pharmacaeutical Industries, Ltd., Israel
Responsible for development of products for the following indications: diabetes, hypertension, epilepsy, cancer, bone disease

COURSES TAKEN:

1. Good Clinical Practice in Clinical Trials
2. Design and Operation of Clinical Trials
3. Monitoring of Clinical Trials
4. International Clinical Studies Management
5. Cost Control, Operation and Strategy

6. Economic Outcomes and Quality of Life
7. Quality Control/Quality Assurance of Clinical Data
8. Safety Reporting in Clinical Trials
9. Pharmacovigilance
10. Statistics for Clinical Trials
11. Senior Managerial Course
12. Strategic Alliances Abroad
12. Business Management – Lahav Business School, Tel Aviv University
13. Companies acquirements and mergers
14. Globalization in Industry
15. Course for Senior Directors in Corporations – Lahav Business School, Tel Aviv University

MEMBERSHIPS

Society for Clinical Trials, Inc.
600 Wyndhurst Avenue
Baltimore, Maryland 21210
U.S.A.

Drug Information Association
3113 Maple Glen, PA 19002
U.S.A.

American Society of Clinical Oncology (ASCO)
1900 Duke Street, Suite 200
Alexandria, VA 22314

American Society for Experimental NeuroTherpeutics (ASENT)
555 E. Wells Street, Suite 1100
Milwaukee, WI 53202-3823

International Society for Quality of Life Research (ISOQOL)
6728 Old McLean Village Drive
McLean, VA 22101-3906
USA

Yafit Stark, Ph.D.

Association of Clinical Research Professionals (ACRP)
Global Headquarters (Washington, DC)
500 Montgomery Street, Suite 800
Alexandria, VA 22314
USA

List of Publications

1. Y. Stark, J. Leibovici and M. Wolman.
Effect of Administration Schedule on Levan the Cyclophosphamide Combined Treatment of Lewis Lung Carcinoma.
Int. J. Immunopharmac. 5:289-297, 1983.

2. J. Leibovici, Y. Stark and M. Wolman.
Combined Effect of Levan and Cytotoxic Agents on the Growth of Experimental Tumors in Mice.
Br. J. Exp. Path. 64:239-244, 1983.

3. J. Leibovici, S. Hoenig, Y. Stark, S. Kopel and M. Wolman.
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Exp. Cell Biol. 52:219-244, 1984.

4. J. Leibovici and Y. Stark.
The Direct Antitumoral Effect of the Polysaccharide Levan: Effects of Drug Concentration, Time and Temperature of Incubation.
J. Natl. Cancer Inst. 72:1417-1420, 1984.

5. M. Michowitz, Y. Stark and J. Leibovii.
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Cancer Lett., 23:343-349, 1984.

6. Y. Stark and J. Leibovici.
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7. J. Leibovici, Y. Stark and S. Kopel.
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8. J. Leibovici and Y. Stark.
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9. Y. Stark and J. Leibovici.

Different Effects of the Polysaccharide Levan on Oncogenecity of Cells of Two Variants of Lewis Lung Carcinoma.
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10. J. Leibovici and Y. Stark.
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11. Y. Stark and J.N. Whitaker.
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12. K.P. Johnson, B.R. Brooks, J.A. Cohen, C.C. Ford et al, and the Copolymer-1 Multiple Sclerosis Study Group.
Copolymer-1 reduces relapse rate and improves disability in relapsing-remitting Multiple Sclerosis. Results of a phase III, multicenter, double-blind, placebo-contolled trial.
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13. K.P. Johnson, B.R. Brooks, J.A. Cohen, C.C. Ford et al, and the Copolymer-1 Multiple Sclerosis Study Group.
Extended use of Glatiramer acetate (Copaxone®) is well tolerated and maintains its clinical effect on Multiple Sclerosis relapse rate and degree of disability.
Neurology, 50: 701-706, 1998.

Submitted for Publication

1. J. Leibovici, Y. Stark, A. Jedeikin.
Combined Hyperthermia - Levan Treatment of Lewis Lung Carcinoma Cells.

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1. J. Leibovici, Y. Stark, T. Eldar, G. Brudner, M. Wolman.
Mechanism of the Inhibitory Effect of Levan in Experimental Tumors. In: Cancer Chemo- and Immunopharmacology 2.
Immunopharmacology, Relation and General Problems.
Recent Results in Cancer Research. Ed. G. Mathe and F.M. Mugia, Springer-Verlag, Berlin, Heidelberg, New York, Vol. 75:173-179, 1980.

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1. Y. Stark, J. Leibovici, M. Michowitz and M. Wolman.
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13th FEBS Meeting, The Federation of European Biochemical Societies, Jerusalem, Israel, p. 186. 1980.

2. J. Leibovici, Y. Stark, S.. Hoenig and M. Wolman.
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3. J. Leibovici, Y. Stark and m. Wolman.
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4. J. Leibovici, Y. Stark and S. Kopel.
Differences in Biological Behavior of Primary and Metastatic AKR Lymphoma Cells.
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5. J. Leibovici and Y. Stark.
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6. J. Leibovici and Y. Stark.
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The Effect of Glatiramer Acetate (Copaxone®) on Disease Activity as

measured by Cerebral MRI in Patients with Relapsing-Remitting Multiple Sclerosis.
ANA, 1998

11. G. Comi, M. Filippi and the Copaxone® MRI Study Group
The Effect of Glatiramer Acetate (Copaxone®) on Disease Activity as measured by Cerebral MRI in Patients with Relapsing-Remitting Multiple Sclerosis.
ANN 1999

12. J.S. Wolinsky, K.P. Johnson, G. Comi, A.E. Miller, D. Ladkani, G. Shifroni, Y. Stark & M. Filippi
Glatiramer Acetate Slows Sustained Accumulated Disability in Relapsing Multiple Sclerosis: Meta-Analysis Results of Three Double-Blind, Placebo-Controlled Clinical Trials
ANN 2003

13. P.K. Coyle, K. Johnson, L. Pardo and Y. Stark, on behalf of the Copaxone Research Team
Pregnancy Outcomes in Patients with Multiple Sclerosis treated with Glatiramer Acetate (Copaxone®)
ANN 2003

14. J.S. Wolinsky, L. Pardo, Y. Stark, S. Silman, S. Kadosh, B. Zak, D. Ladkani and the PROMiSe Study Group
Effect of Glatiramer Acetate on Primary Progressive Multiple Sclerosis: Initial Analysis of the Completed PROMiSe Trial
ANN 2004

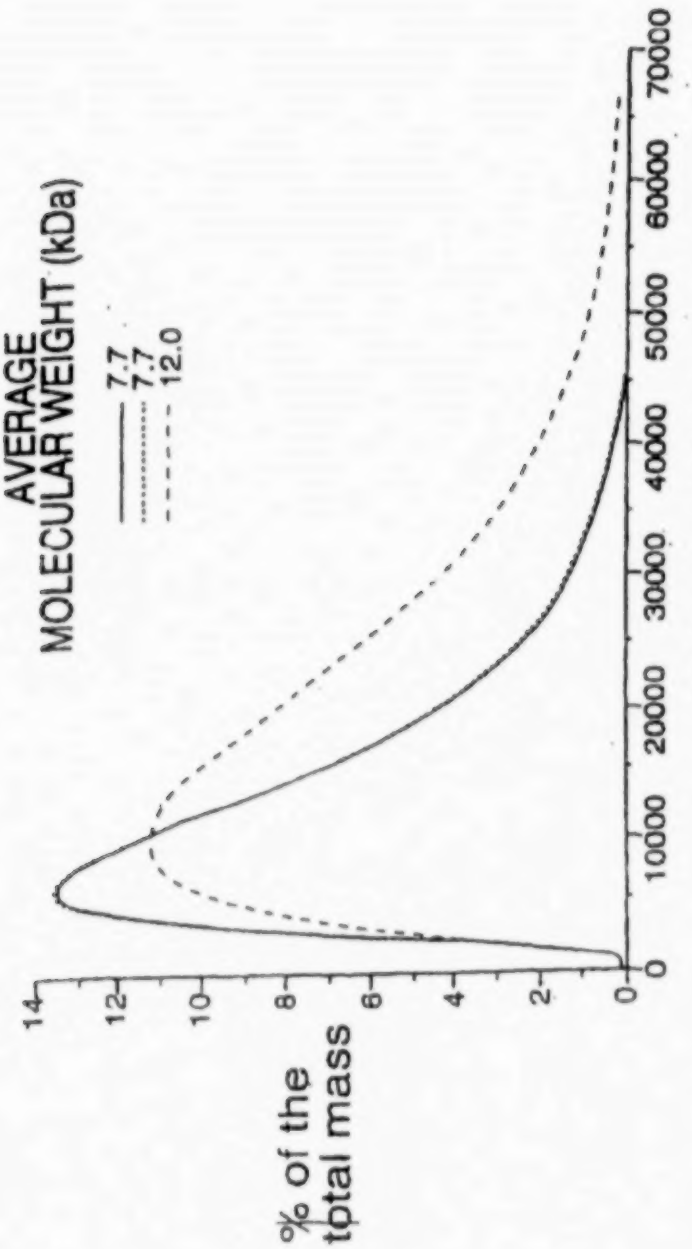
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
% of the
total mass
0
2
4
6
8
10
12
14
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 1

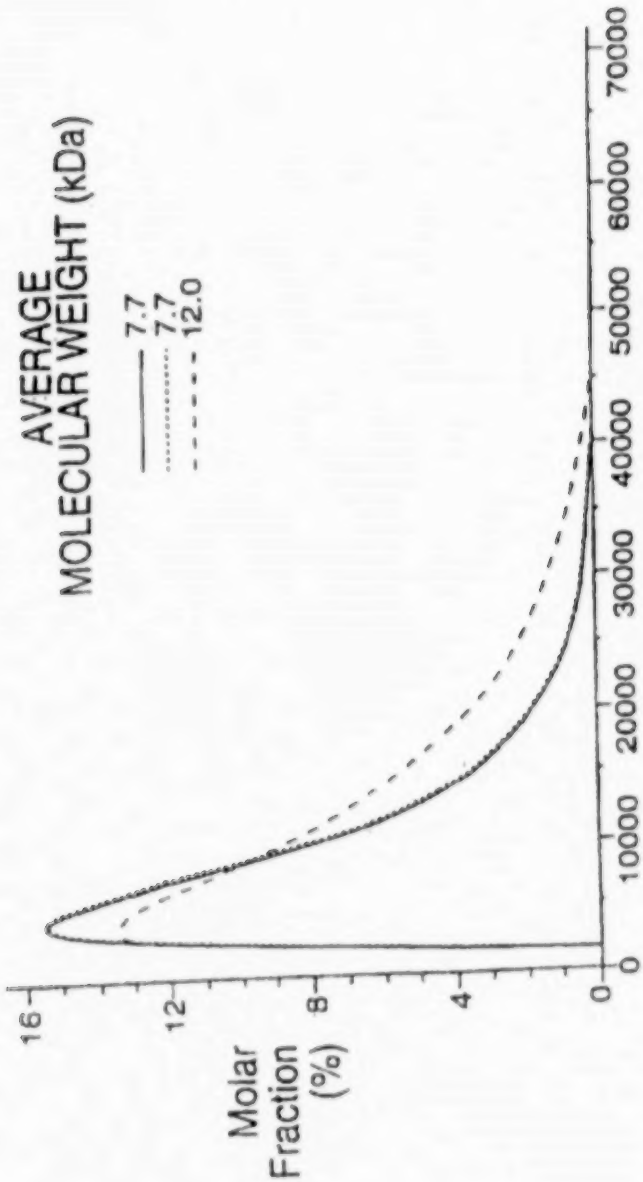
AVERAGE
MOLECULAR WEIGHT (kDa)
7.7
7.7
12.0
Molar
Fraction
(%)
16
12
8
4
0
0
10000
20000
30000
40000
50000
60000
70000
Molecular Weight

FIG. 2

REMARKS

Claims 20-32 are currently pending. Claims 31-32 have been canceled. New claims 33-54 have been added. Thus, upon entry of this amendment, claims 20-30 and 33-54 will be pending.

I. Drawings

Figures 1 and 2, which are incorporated by reference to the parent application, are enclosed herewith for inclusion in the specification. See Exhibit 1.

II. Written Description Rejection

The examiner objects to claim 20 reciting a mixture of polypeptides that is non-uniform with respect to "constitution." Applicants respectfully disagree that this term is unsupported by the specification in view of its ordinary meaning, as set forth in Applicants' previous response. Nonetheless, to expedite allowance, Applicants have amended claim 20 by replacing "constitution" with "sequence," which is a synonymous, non-narrowing term in the context of the specification.

The molecular weight recitation of "about 4 to about 9 kilodaltons" is supported, for example, at p. 2, ll. 18-20 and p. 9, l. 4. The recitation of "about 5 to about 9 kilodaltons" is supported, for example, at p. 9, l. 4.

The examiner states that no support is seen for the specific recitation of a molecular weight "substantially as depicted in the curves of Figure 1 or Figure 2 in which the average molecular weight is about 7.7 kDa." The principal support for this recitation is the figures, which have been incorporated into the specification. In addition, the term "substantially" is an appropriate term of approximation for claiming the curves of the figures for the reasons set forth in section IV, below.

Applicants therefore respectfully request withdrawal of the rejections for lack of written description.

Amendments to the Drawings:

Please add Figures 1 and 2 (attached as Exhibit 1).

III. Enablement Rejection

The examiner acknowledges that the specification is enabling for the use of "copolymer-1", but asserts that it is not enabling for "polypeptides composed of glutamic acid, lysine, alanine and tyrosine." Applicants respectfully disagree. However, to expedite prosecution, Applicants have amended the claims to recite "copolymer-1", the meaning of which is explained below.

The term "copolymer-1," as used in the specification and in the art, refers to a mixture of polypeptides of glutamic acid, lysine, alanine and tyrosine, but is not limited to a specific average molecular weight. In the specification of the pending application, in one instance, citing Teitelbaum et al., Eur. J. Immunol., 1:242-48 (1971), "copolymer-1" refers to a mixture of polypeptides of glutamic acid, lysine, alanine and tyrosine having a molar ratio of about 2 : 4.5 : 6 : 1 and an average molecular weight of about 23 kDa. However, in another instance, the term "copolymer-1" refers to a mixture of polypeptides having a lower average molecular weight, such as the "[f]our batches of copolymer-1, with average molecular weight between 6,250 - 14,500" described in Example 2 of the specification. Thus, "copolymer-1" is not limited to a specific molecular weight.

In addition, the term "copolymer-1" is not limited to a specific molar ratio of amino acids. The molar ratio of the polypeptides of "copolymer-1" varies slightly based on the particular batch and the particular analytical methodology used. In Teitelbaum, for example, two batches of copolymer-1 were prepared at the Weizmann Institute and, using a Beckman-Spinco automatic amino acid analyzer after acid hydrolysis, were determined to contain glutamic acid, lysine, alanine and tyrosine in a molar ratio of either 1.9 : 4.7 : 6.0 : 1.0, or 2.1 : 4.2 : 6.7 : 1.0, respectively. In Bornstein et al., "Clinical Experience with COP-1 in Multiple Sclerosis", N. Engl. J. Med., 317(7):408-14 (1987), three batches of copolymer-1 were obtained from the Weizmann Institute: batch nos. 320, 340 and 400. Citing Teitelbaum, Bornstein states that these three batches contain glutamic acid, lysine, alanine and tyrosine in a molar ratio of 1.9 : 4.7 : 6.0 : 1.0. However, when these batches were retested using total amino acid analysis, a molar ratio of 1.9 : 4.0 : 6.0 : 1.0, or 1.8 : 3.9 : 5.7 : 1.0, or 1.9 : 4.0 : 6.3 : 1.0, respectively, was obtained. Thus, "copolymer-1" does not refer to a specific molar ratio of amino acids.

IV. Indefiniteness Rejections

According to the examiner, the term "constitution" is unclear. For the reasons discussed above, "constitution" has been replaced in the claims by "sequence."

According to the examiner, the term "average molecular weight" is indefinite. Applicants respectfully disagree. One of ordinary skill in the art, upon reviewing the specification, would understand that "average molecular weight" refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1, which is "% of the total mass" versus "molecular weight." As shown in Figure 1, the "average molecular weight" is 7.7 kDa for the separated copolymer-1 ("Batch A") described in Example 1, and 12.0 kDa for the unseparated copolymer-1.

Claims 22 and 27 have been rejected as indefinite in reciting various percentages. Although Applicants respectfully disagree, the phrase "on a molar fraction basis" has been added to these claims. One of ordinary skill in the art would readily recognize that the percentages are molar fractions based on the descriptions in the specification. The table in Example 2, for instance, refers to the "% of species", which would be understood to be a molar fraction.

According to the examiner claim 30 is indefinite for reciting a molecular weight distribution "substantially" as depicted in the curves of Figure 1 or Figure 2. Applicants respectfully disagree. The term "substantially" is definite and appropriate here because a curve based on data points is inherently and inevitably variable to some small degree, and one of ordinary skill in the art would know what "substantially as depicted in the curves" means. See, e.g., MPEP § 2173.05(b)(D); Andrew Corp. v. Gabriel Elecs., Inc., 847 F.2d 819, 821 (Fed. Cir. 1988) (holding a claim not indefinite for reciting an antenna "which produces *substantially equal* E and H plane illumination patterns") (courtesy copy enclosed – see Exhibit 2).

V. Clinical Trials

Applicants have disclosed to the Patent Office, *inter alia*, two clinical trials: "Clinical Trial Protocol No. 9001; first patient enrolled October 23, 1991" and "Clinical Trial Protocol No. 9002; first patient enrolled June 17, 1993," hereinafter referred to as "9001" and "9002",

respectively. These clinical trials were not public uses of the invention. They were experiments related to the development of the invention.

Subsequent to the Third Preliminary Amendment filed April 7, 2004, the Federal Circuit decided SmithKline Beecham Corp. v. Apotex Corp., 365 F.3d 1306 (Fed. Cir. 2004) (hereinafter referred to as "SKB") (courtesy copy enclosed -- see Exhibit 3). The court held, *inter alia*, that a clinical trial in that case was not an experimental use of the invention, but rather a public use under 35 U.S.C. § 102(b). In that case, however, the invention was simply a chemical compound (the entire claim reads "Crystalline paroxetine hydrochloride hemihydrate") "without further limitation regarding efficacy, commercial use, or pharmaceutical viability." Id. at 1318. Based on this claim construction, the court held that the patentee's clinical trial was not a test on claimed features and therefore did not negate a public use. Id. at 1320. The Federal Circuit carefully distinguished narrower claims in the patent which were not asserted in the litigation, stating that clinical trials "may serve to negate a public use bar with regard to the inventions claimed in the more specific claims of the '723 patent." Id. Claim 5 of the '723 patent, for example, is limited to "anti-depressant" pharmaceutical compositions containing "an effective anti-depressant amount of " crystalline paroxetine hydrochloride hemihydrate, and claim 6 is limited to methods of treating depression by administration of "an effective amount" of crystalline paroxetine hydrochloride hemihydrate. *See* U.S. Pat. No. 4,721,723 (courtesy copy enclosed -- see Exhibit 4).

In contrast to the single claim at issue in SKB, Applicants have amended the pending claims to make it even more clear that clinical trials 9001 and 9002 were experimental uses that negate a finding of a public use under 35 U.S.C. § 102(b). The claims are limited to copolymer-1 which is "suitable for treating multiple sclerosis." In SKB, the court noted that an experimental use is one that "improves or verifies a feature [express or] inherent in the express claims of the invention." Id. at 1319. One purpose of clinical trial 9001 was to verify that an improvement in a copolymer-1 composition, reducing toxicity by lowering the average molecular weight, did not diminish or negate the effectiveness of the composition in treating multiple sclerosis. Stark Declaration, ¶ 4 (see Exhibit 5). One purpose of clinical trial 9002 was to collect and verify the

long-term safety of the improved copolymer-1 composition. Stark Declaration, ¶ 5. Thus, clinical trials 9001 and 9002 were necessary to verify the efficacy and pharmaceutical viability of the claimed invention. Stark Declaration, ¶ 6.

VI. Conclusion

Applicants believe that all of the pending claims are in condition for allowance. Any questions should be directed to the undersigned at the telephone number listed below.

Respectfully submitted,

Date: 12/1/04

W. David Wallace
Registration No. 42,210

KENYON & KENYON
1500 K Street, N.W.
Washington, D.C. 20005-1257
Telephone (202) 220-4200
Facsimile (202) 220-4201

DC01 496 075

PATENT APPLICATION SERIAL NO. 10/014,477

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

PTO-1556
(5/87)

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

[redacted]
Bib Data Sheet

CONFIRMATION NO. 1380

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/014,477	12/14/2001 RULE	514	1614	1662/466072

APPLICANTS

Eliezer Konfino, Ramat Gan, ISRAEL;
Michael Sela, Rehovot, ISRAEL;
Dvora Teitelbaum, Rehovot, ISRAEL;
Ruth Arnon, Rehovot, ISRAEL;

** CONTINUING DATA **********

THIS APPLICATION IS A CON OF 09/510,466 02/22/2000 PAT 6,362,161
WHICH IS A CON OF 09/032,334 02/27/1998 PAT 6,048,898
WHICH IS A CON OF 08/447,146 05/22/1995 PAT 5,800,808
WHICH IS A CIP OF 08/344,248 11/23/1994 ABN
WHICH IS A CON OF 08/248,037 05/24/1994 ABN

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 01/04/2002

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☒ no	ISRAEL	2	16	10

35 USC 119 (a-d) conditions met ☐ yes ☒ no ☐ Met after Allowance
Verified and Acknowledged — Examiner's Signature — Initials

ADDRESS

23838

TITLE

Copolymer-1 improvements in compositions of copolymers

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
1328		

* * *

13

ABSTRACT

COPOLYMER-1

IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

* * *

COPOLYMER-1

IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

~~This application is a continuation-in-part of U.S.S.N. 08/344,248, filed November 21, 1994, which is a continuation of U.S.S.N. 08/248,039, filed May 24, 1994.~~

Background of the Invention

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Patent No. 3,849,550) More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar

ratio of approximately 6:2:5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Patent No. 3,849,550)

It is an object of the present invention to provide an improved composition of copolymer-1.

Summary of the Invention

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa)

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

Brief Description of the Drawings

Figure 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40KDa. Figure 2 shows similar data relating to the molar fraction.

Detailed Description of the Invention

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species of copolymer-1 having a molecular weight of 40

KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer 1 having a molecular weight of 40 KDa, or more.

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa. In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Patent 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ-benzyl glutamate and ε-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ-carboxyl group of the glutamic Acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20 to about 26 °C.

The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis

or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection. The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20mg.

The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic method of preparation of low-toxicity copolymer-1 Two batches of copolymer-1 were prepared according to the methods known in the art, for example, U.S. Patent No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 (600 x 26mm) was prepared in a Superformance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20mg/ml, in 0.2N ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having an

relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B: In Vitro

RBL - Degranulation test

I. Introduction

Histamine (or serotonin) release from basophile is an *in vitro* model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-$2H_3$) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (R.L. Basumian, C. Iseraky, M.G. Petrino and R.P. Siraganian. Eur. J. Immunol. 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R.P. Siraganian. Trends in Pharmacological Sciences, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects.

II. Principle of the test method

Rat Basophilic Leukemia cells (RBL-2H$_3$), are loaded with [^{3}H]-serotonin, followed by incubation with 100 µg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [^{3}H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250-14,500 were analyzed for both % of the species with molecular weight over 40KDa and for degranulation of RBL's. Results are summarized in the following table.

Average M.W. (Daltons)	% of species with M.W. over 40KDa	% Serotonin Release
6,250	< 2.5	12.4
7,300	< 2.5	21.0
13,000	> 5	66.9
14,500	> 5	67.8

As can be seen, when the % of high molecular weight species is low (< 2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18g), alanine (50g), γ-benzyl glutamate (35g) and trifluoroacetyllysine

(83g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01 0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6-12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18g), alanine (50g), γ-benzyl glutamate (35g) and trifluoroacetyllysine (83g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01 0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20-28°C a test reaction is performed on every batch at different time periods for example, from 10-50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight 7,000±2,000 Da is calculated from the curve and performed on larger scale reaction. On average, working at 26°C the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of low-toxicity copolymer-1

20g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°-20°C against water until a pH = 8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH = 5.5-6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

CLAIMS

1. A copolymer-1 fraction substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons.

2. A copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons.

3. The copolymer-1 fraction according to claim 2, wherein the fraction contains less than 2.5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons.

4. The copolymer-1 fraction according to claim 2, wherein over 75% of said fraction is within a molecular weight range from about 2 kilodaltons to about 20 kilodaltons.

5. A copolymer-1 fraction, wherein said copolymer-1 has an average molecular weight of about 4 to about 8 kilodaltons.

6. A copolymer-1 fraction, wherein said copolymer-1 has an average molecular weight of about 6.25 to about 8.4 kilodaltons.

7. A composition for the treatment of multiple sclerosis, comprising

a pharmaceutically effective amount of a copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons, and

a pharmaceutically acceptable carrier.

8. The composition according to claim 7, wherein the

copolymer-1 fraction contains less than 2.5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons.

9. The composition according to claim 7, wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons.

10. A composition for the treatment of multiple sclerosis, comprising

a pharmaceutically effective amount of a copolymer-1 fraction, wherein said copolymer-1 in said fraction has an average molecular weight of about 4 to about 8 kilodaltons, and

a pharmaceutically acceptable carrier.

11. A composition for the treatment of multiple sclerosis, comprising

a pharmaceutically effective amount of a copolymer-1 fraction, wherein said copolymer-1 in said fraction has an average molecular weight of about 6.25 to about 8.4 kilodaltons, and

a pharmaceutically acceptable carrier.

12. A method for treating multiple sclerosis, comprising administering to a subject in need thereof a pharmaceutically effective amount of a copolymer-1 fraction, wherein said fraction contains less than 5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons.

13. The method according to claim 12, wherein the copolymer-1 fraction contains less than 2.5% of species of copolymer-1 having a molecular weight of over 40 kilodaltons.

14. The method according to claim 12, wherein over 75% of said copolymer-1 in said fraction is within a molecular weight range of about 2 kilodaltons to about 20 kilodaltons.

15. A method for treating multiple sclerosis, comprising administering to a subject in need thereof a pharmaceutically effective amount of a copolymer-1 fraction, wherein said copolymer-1 in said fraction has an average molecular weight of about 4 to about 8 kilodaltons.

16. A method for treating multiple sclerosis, comprising administering to a subject in need thereof a pharmaceutically effective amount of a copolymer-1 fraction, wherein said copolymer-1 in said fraction has an average molecular weight of about 6.25 to about 8.4 kilodaltons.

* * *

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

DECLARATION AND POWER OF ATTORNEY	ATTORNEY'S DOCKET NO. 1662/466072

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name,

I believe I am an original, first, and joint inventor of the subject matter that is claimed and for which a patent is sought on the invention entitled **COPOLYMER-1: IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS**, the specification of which was filed on May 22, 1995 as Application Serial No. 08/477,146.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

PRIOR UNITED STATES APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION NUMBER	FILING DATE (day, month, year)	STATUS (i.e. Patented, Pending, Abandoned)
08/344,248	23 November 1994	Pending
08/248,837	24 May 1994	Abandoned

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys:

Charles R. Brainard (Reg. No. 21,069)
Alan T. Bowes (Reg. No. 20,306)
Henry S. Hadad (Reg. No. 35,888)

SEND CORRESPONDENCE, AND DIRECT TELEPHONE CALLS TO:

KENYON & KENYON
One Broadway
New York, New York 10004
(212) 425-7200 (phone)
(212) 425-5288 (facsimile)

I declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR	FAMILY NAME KONFINO	FIRST GIVEN NAME Eliezer	SECOND GIVEN NAME
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Signature		Date	

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Signature		Date	
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Signature		Date	

* * *

PRINT OF DRAWINGS
AS ORIGINALLY FILED

Group Art Unit: 1614
Sheet: 1 of 2

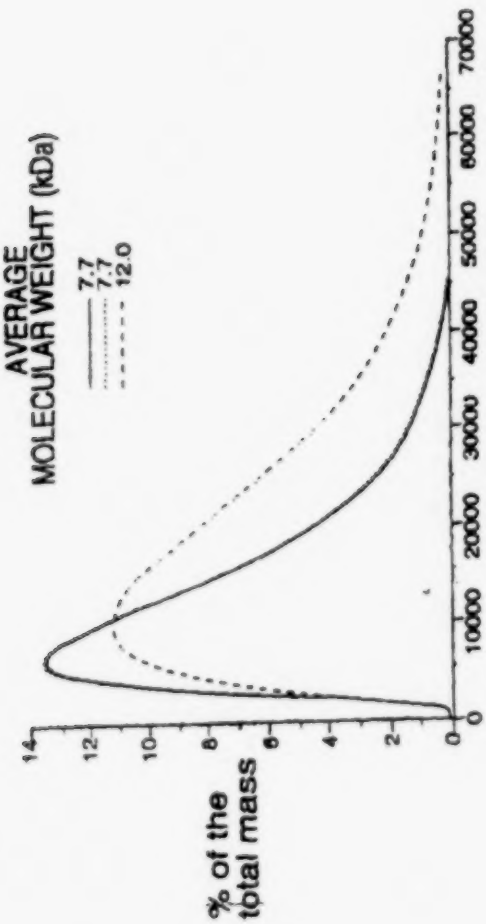

FIG. 1

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AS ORIGINALLY FILED

FIG. 2

* * *

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
[illegible]
Washington, D.C. [illegible]
[illegible]

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
10/014,477	12/14/2001	[illegible]	[illegible]	[illegible]

[illegible] [illegible] [illegible]

KENYON & KENYON
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WASHINGTON, DC 20005

EXAMINER
KRASS, FREDERICK F

ART UNIT	PAPER NUMBER
[illegible]	

DATE MAILED 02/20/2002

3

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 10/014,477	Applicant(s) KONFINO ET AL
	Examiner Frederick Krass	Art Unit 1814

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.

If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.

If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.

Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on ___ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)	4)☐ Interview Summary (PTO-413) Paper No(s). ___
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5)☐ Notice of Informal Patent Application (PTO-152)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). ___	6)☐ Other:

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01) Office Action Summary Part of Paper No. 3

* * *

Indefiniteness Rejection

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1) The term "substantially" free in claim 1 is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a reasonable standard for ascertaining the requisite degree, and thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since no guidance is provided as to how "insubstantially" free of copolymer-1 (COP-1) having a molecular weight of over 40 kilodaltons a given composition may be and still fall within the scope of the instantly claimed subject matter as circumscribed by the term "substantially" free the metes and bounds of the term are not clear, making it impossible to ascertain with reasonable precision when that term is infringed and when it is not.

2) The term "species" in claims 1-3, 7, 8, 12 and 13 is confusing, and hence indefinite, since it is appended to an already definite phrase "copolymer-1" such that it is unclear how or if the former term modifies the latter term. Since the term "species" is not necessary to an understanding of the claimed subject matter, the examiner recommends deleting it.

3) The term "average" molecular weight in claims 5, 6, 10, 11, 15 and 16 is meaningless as a limitation without specifying its basis, e.g. weight average molecular weight, number average molecular weight, etc. (The values for polymer molecular weights will vary according to the type of molecular weight, as anyone skilled in the art will appreciate).

4) The percentage values used throughout the claims are also meaningless without specifying their basis, e.g. percent by weight, percent by mole, percent by volume, etc. Additionally, a frame of reference must be provided, e.g. percent based on the fraction, based on the overall composition, etc.

Anticipation Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 1-4, 7-9 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Tartlebaum et al (USP 3,849,550).

Patentees disclose pharmaceutical compositions for the treatment of multiple sclerosis (column 1, line 30, for example) which contain COP-1 having a molecular weight ranging from more than 10KD (column 1, lines 62 and 63). As anyone of ordinary skill in the art will appreciate, because these are prepared by chemical polymerization (column 2, lines 53-64) they will be polydisperse, i e. they will contain a minor percentage of species above and below the target weight. When that target weight is around 10KD (or even 20KD or 25KD, as disclosed at column 2, line 22), only a very minor proportion (less than 2 5 mole percent) of species over 40KD would be present, and certainly more than 75 mole percent would be in the range of 2 to 20KD.

2) Claims 1-5, 7-10 and 12-16 are rejected under 35 U S.C. 102(b) as being anticipated by European Patent Application 0 383 620.

The prior art discloses pharmaceutical compositions comprising COP-1 for the treatment of multiple sclerosis, wherein the COP-1 has a molecular weight of 5KD (see the first full paragraph on page 3). Since the COP-1 is produced using a biotechnological method (ligation of duplexes) rather than by chemical polymerization, the molecular weight will be extremely narrow and will not deviate substantially from the 5KD value, as anyone of ordinary skill in the art will appreciate.

Obviousness Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 11 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over European Patent Application 0 383 620.

The prior art has been disclosed above and differs from the instant claims in that it does not specify a molecular weight in the range of 6.25 to 8.4 KD.

The determination of *optimal* values within a disclosed range is, however, generally considered obvious. See for example the reasoning set forth by *in re Boesch* 205 USPQ 215. Consonant with the reasoning of such case law, it would have been obvious to have selected a value within the molecular weight range specifically disclosed by the reference (5KD to 50KD, at page 3, line 15), including values within the instantly claimed range of 6.25 to 8.4KD, absent a showing of unexpected results for such selection.

Obviousness-Type Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969)

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 12-16 are rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of U. S. Patent No. 6,342,476. The instant and conflicting claims are clearly coextensive in scope, as is clear from a cursory review of same.

2) Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of U. S. Patent No. 6,054,430. The instant and conflicting claims are clearly coextensive in scope, as is clear from a cursory review of same.

3) Claims 1-8 rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of U. S. Patent No. 5,981,589. The instant and conflicting claims are clearly coextensive in scope, as is clear from a cursory review of same.

Correspondence

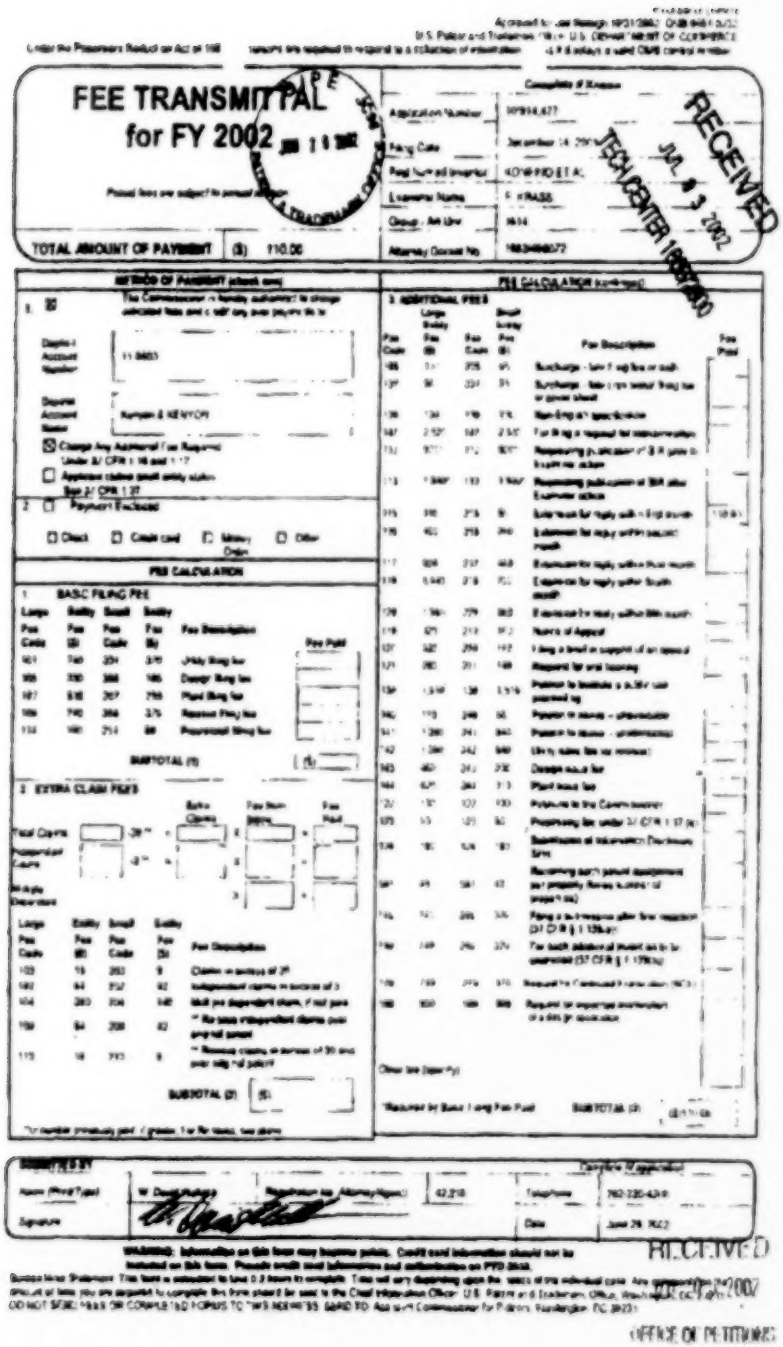
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick Krass whose telephone number is (703) 308-4335. The examiner can normally be reached on Monday, Tuesday and Thursday from 9am to 5pm, on Wednesday from 10:30am to 2:30pm, and on Friday from 11am to 7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0193.

Frederick Krass
Primary Examiner
Art Unit 1614

* * *



FEE TRANSMITTAL
for FY 2002

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JUL 03 2002
TECHCENTER 1600/2900

TOTAL AMOUNT OF PAYMENT ($) 110.00

METHOD OF PAYMENT (check one)

FEE CALCULATION (continued)

FEE CALCULATION

1 BASIC FILING FEE

2 EXTRA CLAIM FEES

3 ADDITIONAL FEES

SUBMITTED BY

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1614
#6
JLP
11/9/02

Patent Docket No.: 1662/4[illegible]72

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TECH CENTER 1600/2900

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors	:	Konfino et al.
Serial No.	:	10/014,477
Filing Date		12/14/01
For		COPOLYMER -1. IMPROVEMENTS IN COMPOSITION OF COPOLYMER
Examiner		F. Krass
Art Unit	:	1614

RECEIVED
JUL 0 5 2002
OFFICE OF PETITIONS

Assistant Commissioner
for Patents
Washington D.C. 20231

AMENDMENT

SIR:

In response to the Office Action dated February 26, 2002, Applicants respectfully request reconsideration of the above-identified application in view of the following amendments and remarks. The fee for a one-month extension of time is enclosed. However, the Commissioner is authorized to charge or debit any underpayment or overpayment to Deposit Account 11-0600.

In the Claims:

Please cancel claims 1-16 without prejudice or disclaimer.

Please add the following new claims:

[illegible] 2002 [illegible] 00000101 110600 10014477
[illegible] 115 [illegible] 110.00 CH

(New) Copolymer-1 having a molecular weight of about 4 to about 9 kilodaltons, made by a process comprising:

treating trifluoroacetyl copolymer-1 with aqueous piperidine to form a solution of copolymer-1; and

B1

purifying copolymer-1, thereby producing copolymer-1 having a molecular weight of about 4 to about 9 kilodaltons

(New) Copolymer-1 made by the process of claim 1, wherein the process further comprises reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1

(New) Copolymer-1 made by the process of claim 18, wherein the hydrobromic acid comprises about 30% hydrogen bromide in acetic acid

(New) Copolymer-1 made by the process of claim 18, wherein the process further comprises polymerizing N-carboxyanhydride derivatives to form protected copolymer-1.

(New) Copolymer-1 made by the process of claim 20, wherein the polymerizing step comprises providing a diethylamine initiator

(New) Copolymer-1 made by the process of claim 18, wherein the process further comprises adding acetic acid subsequent to the treating step

~~(New) Copolymer-1 made by the process of claim 22, wherein the acetic acid displaces substantially all of the trifluoroacetate counter-ions present in the solution of copolymer-1~~

(New) Copolymer-1 made by the process of claim 17, wherein the purifying step comprises filtration

(New) A method of manufacturing trifluoroacetyl copolymer-1 having a predetermined molecular weight profile, comprising the steps of

selecting a predetermined molecular weight profile, and then

reacting protected copolymer-1 with hydrobromic acid at about 26 °C for a time predetermined by test reaction to provide trifluoroacetyl copolymer-1 having the predetermined molecular weight profile

(New) The method of claim 24, further comprising a step of treating the trifluoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile

REMARKS

All of the pending claims, claims 1-16, have been canceled. New claims 17-26 have been added.

Claims 1-16 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully disagree that "molecular weight" and "%" are indefinite. New claim 1 recites "a molecular weight of about 4 to about 9 kilodaltons." One of ordinary skill in the art could understand that kilodalton units implies a weight average molecular weight. Likewise, in the context of the specification and the art, one of ordinary skill in the art would understand that "30% hydrogen bromide in acetic acid" refers to percent by weight.

Claims 1-4, 7-9 and 12-14 have been rejected under 35 U.S.C. § 102(b) as anticipated by Teitelbaum and claims 1-5, 7-10 and 12-16 have been rejected under 35 U.S.C. § 102(b) as anticipated by EP Patent Application 0 383 620. Neither reference, however, recites all of the limitations of the new claims presented. Accordingly, Applicants respectfully request that these rejections be withdrawn.

Claims 6, 11 and 16 have been rejected under 35 U.S.C. § 103(a) as obvious over the EP reference. The Examiner states that it would have been obvious to determine optimal values within a disclosed range. The claimed range, however, shows unexpected results. As shown in Example 2, for instance, the claimed peptides have unexpectedly low toxicity. Applicants therefore respectfully request withdrawal of this rejection.

Claims 12-16 have been rejected for obviousness-type double patenting over U.S. Patent No. 6,342,476 and claims 1-6 have been rejected for obviousness-type double patenting over U.S. Patent No. 6,054,430. These rejections, however, are now moot because these claims have been canceled.

Applicants submit that all of the pending claims of the subject application are now in condition for allowance. Issuance of a Notice of Allowance is respectfully requested. The Examiner is invited to telephone the undersigned attorney at (202) 220-4415 if there are any questions concerning this amendment.

Respectfully submitted,

Date 6/26/02

W. David Wallace (Reg. No. 42,210)

KENYON & KENYON
1500 K Street, NW
Suite 700
Washington, DC 20005

Telephone: (202) 220-4200
Facsimile: (202) 220-4201

* * *

Plaintiffs' Trial Exhibit
CV-08-7611 & CV-09-8824
PTX 19

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 20, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *10/014,477*
FILING DATE: *December 14, 2001*
PATENT NUMBER: *6,620,847*
ISSUE DATE: *September 16, 2003*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

* * *

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,477	12/14/2001	Micret Konfino	1862/466072	1380

23838 7590 02/26/2002

KENYON & KENYON
1500 K STREET, N.W., SUITE 700
WASHINGTON, DC 20005

EXAMINER
KRASS, FREDERICK F

ART UNIT	PAPER NUMBER
1614	3

DATE MAILED: 02/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

P1114[illegible] (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	10/014,477	KONFINO ET AL.	
	Examiner	Art Unit	
	Frederick Krass	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____
4) ☐ Interview Summary (PTO-413) Paper No(s) ____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01) Office Action Summary Part of Paper No. 3

Indefiniteness Rejection

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1) The term "substantially" free in claim 1 is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a reasonable standard for ascertaining the requisite degree, and thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since no guidance is provided as to how "insubstantially" free of copolymer-1 (COP-1) having a molecular weight of over 40 kilodaltons a given composition may be and still fall within the scope of the instantly claimed subject matter as circumscribed by the term "substantially" free the metes and bounds of the term are not clear, making it impossible to ascertain with reasonable precision when that term is infringed and when it is not.

2) The term "species" in claims 1-3, 7, 8, 12 and 13 is confusing, and hence indefinite, since it is appended to an already definite phrase "copolymer-1" such that it is unclear how or if the former term modifies the latter term. Since the term "species" is not necessary to an understanding of the claimed subject matter, the examiner recommends deleting it.

3) The term "average" molecular weight in claims 5, 6, 10, 11, 15 and 16 is meaningless as a limitation without specifying its basis, e.g. weight average molecular weight, number average molecular weight, etc. (The values for polymer molecular weights will vary according to the type of molecular weight, as anyone skilled in the art will appreciate).

4) The percentage values used throughout the claims are also meaningless without specifying their basis, e.g. percent by weight, percent by mole, percent by volume, etc. Additionally, a frame of reference must be provided, e.g. percent based on the fraction, based on the overall composition, etc.

Anticipation Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 1-4, 7-9 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Teitlebaum et al (USP 3,849,550)

Patentees disclose pharmaceutical compositions for the treatment of multiple sclerosis (column 1, line 30, for example) which contain COP-1 having a molecular weight ranging from more than 10KD (column 1, lines 62 and 63). As anyone of ordinary skill in the art will appreciate, because these are prepared by chemical polymerization (column 2, lines 53-64) they will be polydisperse, i.e. they will contain a minor percentage of species above and below the target weight. When that target weight is around 10KD (or even 20KD or 25KD, as disclosed at column 2, line 22), only a very minor proportion (less than 2.5 mole percent) of species over 40KD would be present, and certainly more than 75 mole percent would be in the range of 2 to 20KD.

2) Claims 1-5, 7-10 and 12-16 are rejected under 35 U.S.C. 102(b) as being anticipated by European Patent Application 0 383 620.

The prior art discloses pharmaceutical compositions comprising COP-1 for the treatment of multiple sclerosis, wherein the COP-1 has a molecular weight of 5KD (see the first full paragraph on page 3). Since the COP-1 is produced using a biotechnological method (ligation of duplexes) rather than by chemical polymerization, the molecular weight will be extremely narrow and will not deviate substantially from the 5KD value, as anyone of ordinary skill in the art will appreciate.

Obviousness Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 11 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over European Patent Application 0 383 620.

The prior art has been disclosed above and differs from the instant claims in that it does not specify a molecular weight in the range of 6.25 to 8.4 KD.

The determination of *optimal* values within a disclosed range is, however, generally considered obvious. See for example the reasoning set forth by *in re Boesch* 205 USPQ 215. Consonant with the reasoning of such case law, it would have been obvious to have selected a value within the molecular weight range specifically disclosed by the reference (5KD to 50KD, at page 3, line 15), including values within the instantly claimed range of 6.25 to 8.4KD, absent a showing of unexpected results for such selection.

Obviousness-Type Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 12-16 are rejected under the judicially created doctrine of obviusness-type double patenting over claim 1 of U. S. Patent No. 6,342,476. The instant and conflicting claims are clearly coextensive in scope, as is clear from a cursory review of same.

2) Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of U. S. Patent No. 6,054,430. The instant and conflicting claims are clearly coextensive in scope, as is clear from a cursory review of same.

3) Claims 1-6 rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of U. S. Patent No. 5,[illegible]1,589. The instant and conflicting claims are clearly coextensive in scope, as is clear from a cursory review of same.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick Krass whose telephone number is (703) 308-4335. The examiner can normally be reached on Monday, Tuesday and Thursday from 9am to 5pm, on Wednesday from 10:30am to 2:30pm, and on Friday from 11am to 7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0193.

Frederick Krass
Primary Examiner
Art Unit 1614

* * *

Approved for use through 10/31/2002. OMB 0651-0032
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FEE TRANSMITTAL for FY 2002

JUN 26 2002 PTO
Patent fees are subject to annual revision.

Complete if Known	
Application Number	10/014,477
Filing Date	December 14, 2001
First Named Inventor	KONTIO ET AL
Examiner Name	F. KRASS
Group / Art Unit	1614
Attorney Docket No.	1662/466072

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JUL 03 2002
TECH CENTER 1600/2900

TOTAL AMOUNT OF PAYMENT ($) 110.00

METHOD OF PAYMENT (check one)

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any over payments to

Deposit Account Number: 11-0600

Deposit Account Name: Kenyon & KENYON

☒ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

☐ Applicant claims small entity status. See 37 CFR 1.27

2. ☐ Payment Enclosed

☐ Check ☐ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	150	214	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X =	
Independent Claims		-3** =		X =	
Multiple Dependent				X =	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	110.00
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	330	219	165	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($) 110.00

SUBMITTED BY					Complete (if applicable)
Name (Print/Type)	W. David Hadbavny	Registration No. (Attorney/Agent)	42,210	Telephone	202-220-4200
Signature				Date	June 26, 2002

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Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231

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Patent Docket No.: 1662/4[illegible]72

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors	:	Konfino et al.
Serial No.	:	10/014,477
Filing Date	:	12/14/01
For	:	COPOLYMER -1. IMPROVEMENTS IN COMPOSITION OF COPOLYMER
Examiner	:	F. Krass
Art Unit	:	1614

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OFFICE OF PETITIONS

Assistant Commissioner
for Patents
Washington D.C. 20231

AMENDMENT

SIR:

In response to the Office Action dated February 26, 2002, Applicants respectfully request reconsideration of the above-identified application in view of the following amendments and remarks. The fee for a one-month extension of time is enclosed. However, the Commissioner is authorized to charge or debit any underpayment or overpayment to Deposit Account 11-0600.

In the Claims:

Please cancel claims 1-16 without prejudice or disclaimer.

Please add the following new claims:

07/01/2002 CNGUYEN 00000101 110600 10014477
01 FC:115 110.00 CH

(New) Copolymer-1 having a molecular weight of about 4 to about 9 kilodaltons, made by a process comprising:

treating trifluoroacetyl copolymer-1 with aqueous piperidine to form a solution of copolymer-1; and

purifying copolymer-1, thereby producing copolymer-1 having a molecular weight of about 4 to about 9 kilodaltons.

18. (New) Copolymer-1 made by the process of claim 17, wherein the process further comprises reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1.

19. (New) Copolymer-1 made by the process of claim 18, wherein the hydrobromic acid comprises about 30% hydrogen bromide in acetic acid.

20. (New) Copolymer-1 made by the process of claim 18, wherein the process further comprises polymerizing N-carboxyanhydride derivatives to form protected copolymer-1.

21. (New) Copolymer-1 made by the process of claim 20, wherein the polymerizing step comprises providing a diethylamine initiator.

22. (New) Copolymer-1 made by the process of claim 17, wherein the process further comprises adding acetic acid subsequent to the treating step.

23. ~~(New) Copolymer-1 made by the process of claim 22, wherein the acetic acid displaces substantially all of the trifluoroacetate counter-ions present in the solution of copolymer-1.~~

24. (New) Copolymer-1 made by the process of claim 17, wherein the purifying step comprises filtration.

25. (New) A method of manufacturing trifluoroacetyl copolymer-1 having a predetermined molecular weight profile, comprising the steps of

selecting a predetermined molecular weight profile, and then

reacting protected copolymer-1 with hydrobromic acid at about 26 °C for a time predetermined by test reaction to provide trifluoroacetyl copolymer-1 having the predetermined molecular weight profile.

26. (New) The method of claim 25, further comprising a step of treating the trifluoroacetyl copolymer-1 having the predetermined molecular weight profile with aqueous piperidine solution to form copolymer-1 having the predetermined molecular weight profile.

REMARKS

All of the pending claims, claims 1-16, have been canceled. New claims 17-26 have been added.

Claims 1-16 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully disagree that "molecular weight" and "%" are indefinite. New claim 1 recites "a molecular weight of about 4 to about 9 kilodaltons." One of ordinary skill in the art could understand that kilodalton units implies a weight average molecular weight. Likewise, in the context of the specification and the art, one of ordinary skill in the art would understand that "30% hydrogen bromide in acetic acid" refers to percent by weight.

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Applicants submit that all of the pending claims of the subject application are now in condition for allowance. Issuance of a Notice of Allowance is respectfully requested. The Examiner is invited to telephone the undersigned attorney at (202) 220-4415 if there are any questions concerning this amendment.

Respectfully submitted,

Date: 6/26/02

W. David Wallace (Reg. No 42,210)

KENYON & KENYON
1500 K Street, NW
Suite 700
Washington, DC 20005

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* * *

UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,477	12/14/2001	Ehrenz Kenfino	1562/46072	1380

21838 7590 12/03/2002

KENYON & KENYON
1500 K STREET, N.W., SUITE 700
WASHINGTON, DC 20005

EXAMINER
KRASS, FREDERICK F

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 12/03/2002

#8

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)
	10/014,477	KONFINO ET AL.
	Examiner	Art Unit
	Frederick Krass	1614

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 17-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 17-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other.

Previous Rejections

All previous rejections are withdrawn, unless explicitly repeated hereinunder.

Informalities

The fifth line of claim 25 contains an obvious spelling incorrection.

New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

* * *

Notice of Allowability	Application No. 10/014,477	Applicant(s) KONFINO ET AL.	
	Examiner Frederick Krass	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS. This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the request for reconsideration dated April 2, 2003
2. ☒ The allowed claim(s) is/are 17-22 and 24-26
3. ☒ The drawings filed on 14 December 2001 are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____.
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received. _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

8. ☐ CORRECTED DRAWINGS must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the top margin (not the back) of each sheet. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☐ Interview Summary (PTO-413), Paper No. ____.
5☐ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☐ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☐ Examiner's Statement of Reasons for Allowance
9☐ Other

FREDERICK KRASS
PRIMARY EXAMINER

U.S. Patent and Trademark Office
PTO-37 (Rev. 04-01) Notice of Allowability Part of Paper No. 12

* * *

Plaintiffs' Trial Exhibit
CV-08-7611 & CV-09-8824
PTX 20

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

March 18, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *10/615,865*
FILING DATE: *July 10, 2003*
PATENT NUMBER: *6939539*
ISSUE DATE: *September 06, 2005*

Certified by

W. Dudas

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

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Fax Transmission

From: David Wallace Date April 7, 2004

Direct Dial: 202.220.4415 Fax: 202.220.4201

Client/Matter: New U.S. Patent Application
Serial No.: 10/615,865
Our Ref.: 1662/466073

Total number of pages: [redacted]
(including cover)

Please deliver to:

Name	Company	Fax	Phone
Examiner F. Krass	U.S. Patent and Trademark Office	703-872-9306	

Dear Examiner Krass:

Attached is a courtesy copy of the Preliminary Amendment filed with the U.S. Patent and Trademark Office today.

David Wallace

489318

☒ Original will not follow ☐ Original will follow by ☐ Regular Mail ☐ Overnight Delivery ☐ Hand Delivery

The information contained in this facsimile transmission, including any attachments, is subject to the attorney-client privilege, the attorney work product privilege or is confidential information intended only for the use of the named recipient. If the reader of this Notice is not the intended recipient or the employee or agent responsible for delivering this transmission to the intended recipient, you are hereby notified that any use, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this transmission in error, please notify us immediately by telephone, so that we may arrange for its return or destruction at our cost. Thank you.

PAGE 1/8 * RCVD AT 4/7/2004 4:23:42 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/2 * DNIS:2729306 * CSID:202 220 4201 * DURATION (mm-ss):02-56

OFFICIAL

PATENT
1662/466073

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APPLICANTS	KONFINO et al.
APPLICATION SERIAL NO.	10/615,865
FILED	July 9, 2003
FOR	COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS
EXAMINER	Examiner P. Krass
GROUP ART UNIT	1614

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

THIRD PRELIMINARY AMENDMENT

Sir:

Prior to examination of this application, please consider the pending claims in view of the amendments and remarks set forth herein. No fee is believed due.

PAGE 2/8 * RCVD AT 4/7/2004 4:23:42 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:202 220 4201 * DURATION (mm-ss):02-56

Listing of Claims:

Claims 1-19 (Canceled)

20. (Amended) A composition comprising a polydisperse mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, and wherein the mixture of polypeptides is non uniform with respect to molecular weight and constitution

21. (Previously presented) The composition of claim 20, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

22. (Previously presented) The composition of claim 20, wherein less than 5% of the polypeptides of the mixture have a molecular weight of over 40 kilodaltons.

23. (Previously presented) The composition of claim 22, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

24. (Previously presented) The composition of claim 23, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons

25 (Previously presented) The composition of claim 20, wherein the mixture has an average molecular weight of about 4 to about 8 6 kilodaltons.

26. (Previously presented) The composition of claim 20, wherein the mixture has an average molecular weight of about 5 to about 9 kilodaltons.

PAGE 38 * RCVD AT 4/7/2004 4:22:42 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:202 220 4201 * DURATION (mm-ss):02-58

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27. (Previously presented) The composition of claim 20, wherein less than 2.5% of the polypeptides of the mixture have a molecular weight of over 40 kilodaltons.

28. (Previously presented) The composition of claim 27, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

29. (Previously presented) The composition of claim 28, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

30. (Previously presented) The composition of claim 20, wherein the mixture has a molecular weight distribution substantially as depicted in the curves of Figure 1 or Figure 2 in which the average molecular weight is about 7.7 kDa.

31. (Previously presented) A pharmaceutical composition comprising a dose therapeutically effective to treat multiple sclerosis of the composition of any of claims 20-30.

32. (Previously presented) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the composition of claim 31.

PAGE 4/8 * RCVD AT 4/7/2004 4:23:42 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:202 220 4201 * DURATION (mm-ss):02-56

TEV000304639

REMARKS

Applicants would like to thank the examiner for extending the courtesy of a personal interview on March 15, 2004. During the interview, it was agreed that neither the '550 patent to Teitelbaum nor the EP '620 publication would anticipate or render obvious the claimed invention, provided that the pending claims be amended to recite that the mixture of polypeptides is non-uniform with respect to molecular weight and constitution. Applicants herein amend claim 20, the sole independent claim, and set forth below the inherent support in the specification for the amendment. In view of the amendment, the term "polydisperse" is now redundant and therefore unnecessary, it has therefore been deleted from the claims.

In addition, filed concurrently herewith is a terminal disclaimer to obviate possible obviousness-type double patenting rejections over prior patents. In accordance with the examiner's suggestion, we have included in the disclaimer all of Teva's issued U.S. patents in this family, i.e., 5,800,808, 5,981,589, 6,048,898, 6,054,430, 6,342,476, 6,362,161, and 6,620,847.

Claims 20-32 are pending in the application. Claim 20 has been amended to further clarify that the mixture is non-uniform with respect to both molecular weight and constitution. Support for the recitation "wherein the mixture of polypeptides is non-uniform with respect to molecular weight and constitution" can be found throughout the specification. For example, col. 1, l. 49-51, recites an embodiment having over 75% of its molar fraction within the molecular weight range from about 2-20 kDa. This shows that a preferred composition contains polypeptide species of non-uniform molecular weight. The molecular weight distributions shown in Figs. 1 and 2 further evidence that the polypeptide species in this mixture are of non-uniform molecular weight.

It is also readily apparent to one of ordinary skill in the art that embodiments of the invention include polypeptide species of non-uniform constitution. Copolymer-1 batches were prepared by chemically polymerizing alanine, glutamic acid, lysine, and tyrosine. Col. 1, ll. 36-41. After reading the specification, one of ordinary skill in the art would understand, based on the disclosed method of preparation, that the polypeptides in the copolymer-1 batches are of non-uniform constitution. In Example 1, for instance, "[t]wo batches of copolymer-1 were prepared

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according to the methods known in the art, for example, U.S. Pat. No. 3,849,550." Col. 2, ll. 55-58. EP application 0 383 620 explicitly notes that the synthesis of copolymer-1 according to the '550 patent produces polypeptides that are non-uniform in constitution: "Although the resulting polypeptides are comprised of the same amino acid components, they differ with respect to their amino acid sequences." EP '620, p. 2, ll. 19-21.

The phrase "non-uniform with respect to molecular weight and constitution" may be used in the claims even if that phrase is not expressly stated in the specification because claim language does not require *ipsis verbis* support in the specification. "Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question." Fujikawa v. Wattanasin, 93 F.3d 1559, 1570 (Fed. Cir. 1996); *see also* Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1565 (Fed. Cir. 1991) (holding that drawings alone may provide a "written description" of the invention). Therefore, because the recited phrase "non-uniform with respect to molecular weight and constitution" is clearly supported by the specification, this phrase has written description support under 35 U.S.C. § 112, first paragraph.

Applicants believe that all of the pending claims are in condition for allowance. Any questions should be directed to the undersigned at the telephone number listed below.

Respectfully submitted,

Date: 4/7/04

By: _____
W. David Wallace
Registration No. 42,210

KENYON & KENYON
1500 K Street, N.W.
Suite 700
Washington, D.C. 20005-1257
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Facsimile (202) 220-4201

DC01 485 740

PAGE 6/8 * RCVD AT 4/7/2004 4:22:42 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID:202 220 4201 * DURATION (mm-ss):02-58

* * *

TEV000304641

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,865	07/10/2003	Eliezer Kanfano	1662/466073	8419

23838 7590 08/01/2004

KENYON & KENYON
1500 K STREET, N.W., SUITE 700
WASHINGTON, DC 20005

EXAMINER	
KRASS, FREDERICK F	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/615,865	KONFINO ET AL.	
	Examiner	Art Unit	
	Frederick F. Krass	1614	

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Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
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- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
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Status

1)☒ Responsive to communication(s) filed on *07 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 20-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 20-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

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2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-7-04*

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

Drawings

Insofar as the examiner can determine, no copy of Figures 1 and 2 is present in the IFW application. Applicant is requested to resubmit same.

Written Description ("New Matter") Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

1) The specification as originally filed does not describe, implicitly or explicitly, compositions comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture of polypeptides is non-uniform with respect to

"constitution", as recited in claim 20. (See the detailed discussion in the related rejection at subsection "1)" of the "Indefiniteness" section hereinunder).

2) Where the PTO has sufficient reason to doubt that a broader described range pertains to the same invention than a narrower (and subsumed) claimed range, then the broader range does not describe the narrower range. In re Wertheim, 541 F.2d 257, 264-265 (CCPA 1976). (Holding that, in light of the description of the invention as employing as employing a solids content in the range of 25-65%, along with specific embodiments of 36% and 50%, the PTO would not have such reason to doubt since persons skilled in the art would consider processes employing a range of 35-60% to be part of the claimed invention). Merely amending claims to conform to values disclosed by the prior art without any originally disclosed basis for narrowing applicant's disclosed range, however, provides sufficient reason to doubt that the originally disclosed broader range does not described the newly claimed narrower range. In re Baird, 348 F.2d 974, 982 (CCPA 1965).

Accordingly, no support is seen in the specification as originally filed for claiming the specific range "about 4 to about 9 kilodaltons" in claim 20, and "about 5 to about 9 kilodaltons" in claim 26. Similarly, no support is seen for the specific recitation of a molecular weight "substantially as depicted in the curves of Figure 1 or Figure 2 in which the average molecular weight is about 7.7 kDa."

Scope of Enablement Rejection

Claims 20-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of Copolymer-1, does not reasonably provide enablement for using polypeptides "composed of glutamic acid, lysine, alanine and tyrosine". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1. The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art

The invention relates to certain "COP-1" polypeptides, well-known in the art. The relative skill of those in the art is high, generally that of a PHD or MD. This high level of skill, however, is outweighed by the recognized unpredictability of the art.

As is well-known, Copolymer-1 ("COP-1") is a synthetic polypeptide analog of myelin basic protein, having the biological activity of treating multiple sclerosis. It is a complex mixture of polypeptides made by polymerizing alanine, glutamic acid, lysine and tyrosine in a molar ratio of approximately 6:2.5:1, to form products having an average molecular weight of 23,000 daltons. See the instant specification at page 1, lines 8-10, and at the passage spanning page 1, line 32 to page 2, line 4. Such polymerization results in an extremely complex mixture of products, varying both in molecular weight and amino acid sequence. It is unknown, however, which particular product or products within the mixture is responsible for its biological activity. The incorporation of other amino acids likewise has an unpredictable effect on biological activity. See European Patent Application 0 383 620 A2 at page 2, lines 17-30.

2. The breadth of the claims

The rejected claims are extremely broad and inclusive of all polypeptides of alanine, glutamic acid, lysine and tyrosine having a molecular weight between 5 and 9

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kilodaltons, irrespective of the relative molar proportions of each amino acid. The claims are also permit the inclusion of other amino acids.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no guidance for preparing mixtures of polypeptides of alanine, glutamic acid, lysine and tyrosine having the requisite biological activity of treating multiple sclerosis, other than COP-1 (the only species used in the working examples).

4. The quantity of experimentation necessary

Applicant fails to provide information allowing the skilled artisan to ascertain which particular polypeptides comprising alanine, glutamic acid, lysine and tyrosine, other than COP-1 (i.e. the polymerization product of only those four amino acids in the molar ratio of approximately 6:2:5:1) can be used in the instant invention, i.e. to carry out the disclosed utility of the claimed invention, the treatment of multiple sclerosis. The biological activity of such polypeptides is highly unpredictable, and must be determined empirically on a case-by-case basis, with no a priori expectation of success. In the instant case, only one species, COP-1, is exemplified in the working examples. By contrast, the instant claims are very broad and read on polypeptides made from alanine,

glutamic acid, lysine and tyrosine in any relative proportions, and additionally species in which other amino acids could be incorporated. This encompasses an overwhelming number of possible combinations and thus necessitates an exhaustive and undue search for all the embodiments suitable to practice the claimed invention. Given the sheer number of potential combinations of amino acids, and the recognized unpredictability of this art, one would have to mount a massive additional research campaign to determine which combinations within the scope of the instant claims would exhibit the required characteristics. Accordingly, applicant has failed to provide information sufficient to practice the claimed invention absent resorting to undue experimentation.

Indefiniteness Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1) The scope of the term "constitution" (claim 20, last line) is entirely unclear. While one can reasonably infer from the specification (as discussed by Applicant in his

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preliminary comments) that the instantly claimed polypeptides will vary in molecular weight and amino acid sequence, that is not the same as a mixture's "constitution". That term is essentially subjective in nature; there is no recognized parameter by which a composition's "constitution" can be measured, making it impossible to determine the metes and bounds of the claimed term.

2) Where a claimed value varies with its method of measurement and several alternative methods of measurement are available, the claimed value is indefinite without knowing which method of measurement was used. Honeywell Intl., Inc. v. Intl. Trade Commn., 341 F.3d 1332, 1340 (Fed. Cir. 2003). Accordingly, the term "average molecular weight" (claim 20, second and third lines; claims 24-26; and claim 29) is indefinite since its method of measurement is not specified, i.e. number average molecular weight, weight average molecular weight, average molecular weight as determined by light scattering, etc.

3) Similarly, the percentage values recited in claims 22 and 27 are indefinite without knowing which method was used to compute them, i.e. percent by weight, percent by mole, percent by volume, etc.

4) The term "substantially" in claim 30 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not

provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Allowable Subject Matter

Claims 20-32 would be allowable if amended to overcome the outstanding rejections under 35 U.S.C. 112.

The terminal disclaimer submitted by Applicant has been accepted.

The closest prior art of record is European Patent Application 0 383 620 A2, which discloses COP-1 which is produced by recombinant DNA technology. The polypeptides resulting from this process will be uniform in molecular weight and amino acid sequence, and the individual uniform polypeptides can be pooled to form non-uniform mixtures for activity studies. See the first paragraph of page 3. The individual uniform polypeptides may have a lower molecular weight limit of 5 kilodaltons (page 3, line 15), but the prior art provides no direction for pooling such lower molecular weight species to form a non-uniform mixture. Instead, it directs away from same, teaching testing mixtures having much higher molecular weights, on the order of 15-23 kilodaltons. (See page 5, lines 28-34, for example). By contrast, Applicant has factually demonstrated that lower molecular weight Cop-1 has unexpectedly lowered side effects (see pages 5-9 of the instant specification).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick F. Krass whose telephone number is 571-272-0580. The examiner's schedule is as follows:

Monday: 6:30-3:00PM;
Tuesday: 10-6:30PM;
Wednesday: off;
Thursday: 10-6:30PM; and
Friday: 10-6:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Seidel Marianne, can be reached on 571-272-0584. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frederick Krass
Primary Examiner
Art Unit 1614

* * *

Listing of Claims:

Claims 1-19 (Canceled).

20. (Currently amended) A copolymer-1 composition comprising a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, ~~and~~ wherein the mixture of polypeptides is non-uniform with respect to molecular weight and ~~constitution~~ sequence, and wherein the composition is suitable for treating multiple sclerosis.

21. (Previously presented) The composition of claim 20, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

22. (Currently amended) The composition of claim 20, wherein less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

23. (Previously presented) The composition of claim 22, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

24. (Previously presented) The composition of claim 23, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

25. (Previously presented) The composition of claim 20, wherein the mixture has an average molecular weight of about 4 to about 8.6 kilodaltons.

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26. (Previously presented) The composition of claim 20, wherein the mixture has an average molecular weight of about 5 to about 9 kilodaltons.

27. (Currently amended) The composition of claim 20, wherein less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

28. (Previously presented) The composition of claim 27, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

29. (Previously presented) The composition of claim 28, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

30. (Previously presented) The composition of claim 20, wherein the mixture has a molecular weight distribution substantially as depicted in the curves of Figure 1 or Figure 2 in which the average molecular weight is about 7.7 kDa.

31. (Canceled)

32. (Canceled)

33. (New) A pharmaceutical composition comprising:

a dose therapeutically effective to treat multiple sclerosis of a copolymer-1 composition, wherein the copolymer-1 composition comprises a mixture of polypeptides composed of glutamic acid, lysine, alanine and tyrosine, wherein the mixture has an average molecular weight of about 4 to about 9 kilodaltons, wherein the mixture of polypeptides is non-uniform with respect to molecular weight and sequence; and

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a pharmaceutically acceptable excipient.

34. (New) The pharmaceutical composition of claim 33, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

35. (New) The pharmaceutical composition of claim 33, wherein less than 5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

36. (New) The pharmaceutical composition of claim 35, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

37. (New) The pharmaceutical composition of claim 36, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

38. (New) The pharmaceutical composition of claim 33, wherein the mixture has an average molecular weight of about 4 to about 8.6 kilodaltons.

39. (New) The pharmaceutical composition of claim 33, wherein the mixture has an average molecular weight of about 5 to about 9 kilodaltons.

40. (New) The pharmaceutical composition of claim 33, wherein less than 2.5% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight of over 40 kilodaltons.

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41. (New) The pharmaceutical composition of claim 40, wherein over 75% of the polypeptides of the mixture, on a molar fraction basis, have a molecular weight in a range of about 2 kilodaltons to about 20 kilodaltons.

42. (New) The pharmaceutical composition of claim 41, wherein the mixture has an average molecular weight of 6.25 to 8.4 kilodaltons.

43. (New) The pharmaceutical composition of claim 33, wherein the mixture has a molecular weight distribution substantially as depicted in the curves of Figure 1 or Figure 2 in which the average molecular weight is about 7.7 kDa.

44. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 33.

45. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 34.

46. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 35.

47. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 36.

48. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 37.

49. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 38.

50. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 39.

51. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 40.

52. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 41.

53. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 42.

54. (New) A method for treating a patient suffering from multiple sclerosis comprising administering to a patient in need thereof the pharmaceutical composition of claim 43.

PATENT
1662/466073

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	KONFINO et al.
APPLICATION SERIAL NO:		10/615,865
FILED	:	July 9, 2003
FOR	:	COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS
EXAMINER	:	Examiner F. Krass
GROUP ART UNIT	:	1614

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

In response to the office action dated June 1, 2004, Applicants respectfully request reconsideration in view of the following amendments and remarks. The fee for a three-month extension of time is enclosed. However, the Commissioner is hereby authorized to charge any payment due in connection with these papers, or credit any overpayment, to Deposit Account No. 11-0600.

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* * *

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REMARKS

Claims 20-32 are currently pending. Claims 31-32 have been canceled. New claims 33-54 have been added. Thus, upon entry of this amendment, claims 20-30 and 33-54 will be pending.

I. Drawings

Figures 1 and 2, which are incorporated by reference to the parent application, are enclosed herewith for inclusion in the specification. See Exhibit 1.

II. Written Description Rejection

The examiner objects to claim 20 reciting a mixture of polypeptides that is non-uniform with respect to "constitution." Applicants respectfully disagree that this term is unsupported by the specification in view of its ordinary meaning, as set forth in Applicants' previous response. Nonetheless, to expedite allowance, Applicants have amended claim 20 by replacing "constitution" with "sequence," which is a synonymous, non-narrowing term in the context of the specification.

The molecular weight recitation of "about 4 to about 9 kilodaltons" is supported, for example, at p. 2, ll. 18-20 and p. 9, l. 4. The recitation of "about 5 to about 9 kilodaltons" is supported, for example, at p. 9, l. 4.

The examiner states that no support is seen for the specific recitation of a molecular weight "substantially as depicted in the curves of Figure 1 or Figure 2 in which the average molecular weight is about 7.7 kDa." The principal support for this recitation is the figures, which have been incorporated into the specification. In addition, the term "substantially" is an appropriate term of approximation for claiming the curves of the figures for the reasons set forth in section IV, below.

Applicants therefore respectfully request withdrawal of the rejections for lack of written description.

Amendments to the Drawings:

Please add Figures 1 and 2 (attached as Exhibit 1).

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III. Enablement Rejection

The examiner acknowledges that the specification is enabling for the use of "copolymer-1", but asserts that it is not enabling for "polypeptides composed of glutamic acid, lysine, alanine and tyrosine." Applicants respectfully disagree. However, to expedite prosecution, Applicants have amended the claims to recite "copolymer-1", the meaning of which is explained below.

The term "copolymer-1," as used in the specification and in the art, refers to a mixture of polypeptides of glutamic acid, lysine, alanine and tyrosine, but is not limited to a specific average molecular weight. In the specification of the pending application, in one instance, citing Teitelbaum et al., Eur. J. Immunol., 1:242-48 (1971), "copolymer-1" refers to a mixture of polypeptides of glutamic acid, lysine, alanine and tyrosine having a molar ratio of about 2 : 4.5 : 6 : 1 and an average molecular weight of about 23 kDa. However, in another instance, the term "copolymer-1" refers to a mixture of polypeptides having a lower average molecular weight, such as the "[f]our batches of copolymer-1, with average molecular weight between 6,250 - 14,500" described in Example 2 of the specification. Thus, "copolymer-1" is not limited to a specific molecular weight.

In addition, the term "copolymer-1" is not limited to a specific molar ratio of amino acids. The molar ratio of the polypeptides of "copolymer-1" varies slightly based on the particular batch and the particular analytical methodology used. In Teitelbaum, for example, two batches of copolymer-1 were prepared at the Weizmann Institute and, using a Beckman-Spinco automatic amino acid analyzer after acid hydrolysis, were determined to contain glutamic acid, lysine, alanine and tyrosine in a molar ratio of either 1.9 : 4.7 : 6.0 : 1.0, or 2.1 : 4.2 : 6.7 : 1.0, respectively. In Bornstein et al., "Clinical Experience with COP-1 in Multiple Sclerosis", N. Engl. J. Med., 317(7):408-14 (1987), three batches of copolymer-1 were obtained from the Weizmann Institute: batch nos. 320, 340 and 400. Citing Teitelbaum, Bornstein states that these three batches contain glutamic acid, lysine, alanine and tyrosine in a molar ratio of 1.9 : 4.7 : 6.0 : 1.0. However, when these batches were retested using total amino acid analysis, a molar ratio of 1.9 : 4.0 : 6.0 : 1.0, or 1.8 : 3.9 : 5.7 : 1.0, or 1.9 : 4.0 : 6.3 : 1.0, respectively, was obtained. Thus, "copolymer-1" does not refer to a specific molar ratio of amino acids.

IV. Indefiniteness Rejections

According to the examiner, the term "constitution" is unclear. For the reasons discussed above, "constitution" has been replaced in the claims by "sequence."

According to the examiner, the term "average molecular weight" is indefinite. Applicants respectfully disagree. One of ordinary skill in the art, upon reviewing the specification, would understand that "average molecular weight" refers to the molecular weight at the peak of the molecular weight distribution curve shown in Figure 1, which is "% of the total mass" versus "molecular weight." As shown in Figure 1, the "average molecular weight" is 7.7 kDa for the separated copolymer-1 ("Batch A") described in Example 1, and 12.0 kDa for the unseparated copolymer-1.

Claims 22 and 27 have been rejected as indefinite in reciting various percentages. Although Applicants respectfully disagree, the phrase "on a molar fraction basis" has been added to these claims. One of ordinary skill in the art would readily recognize that the percentages are molar fractions based on the descriptions in the specification. The table in Example 2, for instance, refers to the "% of species", which would be understood to be a molar fraction.

According to the examiner claim 30 is indefinite for reciting a molecular weight distribution "substantially" as depicted in the curves of Figure 1 or Figure 2. Applicants respectfully disagree. The term "substantially" is definite and appropriate here because a curve based on data points is inherently and inevitably variable to some small degree, and one of ordinary skill in the art would know what "substantially as depicted in the curves" means. See, e.g., MPEP § 2173.05(b)(D); Andrew Corp. v. Gabriel Elecs., Inc., 847 F.2d 819, 821 (Fed. Cir. 1988) (holding a claim not indefinite for reciting an antenna "which produces *substantially equal* E and H plane illumination patterns") (courtesy copy enclosed – see Exhibit 2).

V. Clinical Trials

Applicants have disclosed to the Patent Office, *inter alia*, two clinical trials: "Clinical Trial Protocol No. 9001; first patient enrolled October 23, 1991" and "Clinical Trial Protocol No. 9002; first patient enrolled June 17, 1993," hereinafter referred to as "9001" and "9002",

respectively. These clinical trials were not public uses of the invention. They were experiments related to the development of the invention.

Subsequent to the Third Preliminary Amendment filed April 7, 2004, the Federal Circuit decided SmithKline Beecham Corp. v. Apotex Corp., 365 F.3d 1306 (Fed. Cir. 2004) (hereinafter referred to as "SKB") (courtesy copy enclosed – see Exhibit 3). The court held, *inter alia*, that a clinical trial in that case was not an experimental use of the invention, but rather a public use under 35 U.S.C. § 102(b). In that case, however, the invention was simply a chemical compound (the entire claim reads "Crystalline paroxetine hydrochloride hemihydrate") "without further limitation regarding efficacy, commercial use, or pharmaceutical viability." Id. at 1318. Based on this claim construction, the court held that the patentee's clinical trial was not a test on claimed features and therefore did not negate a public use. Id. at 1320. The Federal Circuit carefully distinguished narrower claims in the patent which were not asserted in the litigation, stating that clinical trials "may serve to negate a public use bar with regard to the inventions claimed in the more specific claims of the '723 patent." Id. Claim 5 of the '723 patent, for example, is limited to "anti-depressant" pharmaceutical compositions containing "an effective anti-depressant amount of " crystalline paroxetine hydrochloride hemihydrate, and claim 6 is limited to methods of treating depression by administration of "an effective amount" of crystalline paroxetine hydrochloride hemihydrate. *See* U.S. Pat. No. 4,721,723 (courtesy copy enclosed -- see Exhibit 4).

In contrast to the single claim at issue in SKB, Applicants have amended the pending claims to make it even more clear that clinical trials 9001 and 9002 were experimental uses that negate a finding of a public use under 35 U.S.C. § 102(b). The claims are limited to copolymer-1 which is "suitable for treating multiple sclerosis." In SKB, the court noted that an experimental use is one that "improves or verifies a feature [express or] inherent in the express claims of the invention." Id. at 1319. One purpose of clinical trial 9001 was to verify that an improvement in a copolymer-1 composition, reducing toxicity by lowering the average molecular weight, did not diminish or negate the effectiveness of the composition in treating multiple sclerosis. Stark Declaration, ¶ 4 (see Exhibit 5). One purpose of clinical trial 9002 was to collect and verify the

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long-term safety of the improved copolymer-1 composition. Stark Declaration, ¶ 5. Thus, clinical trials 9001 and 9002 were necessary to verify the efficacy and pharmaceutical viability of the claimed invention. Stark Declaration, ¶ 6.

VI. Conclusion

Applicants believe that all of the pending claims are in condition for allowance. Any questions should be directed to the undersigned at the telephone number listed below.

Respectfully submitted,

Date: 12/1/97

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* * *

TEV000304805

Notice of Allowability	Application No.	Applicant(s)	
	10/615,865	KONFINO ET AL.	
	Examiner	Art Unit	
	Amy A. Lewis	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the remarks and amendments file 1 December 2004*.

2. ☒ The allowed claim(s) is/are *20-30 and 33-54*.

3. ☒ The drawings filed on *01 December 2004* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____.
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

PETITIONER'S BRIEF

No. 13-854

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

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June 13, 2014

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QUESTION PRESENTED

Rule 52(a) of the Federal Rules of Civil Procedure provides that in matters tried to a district court, the court's "[f]indings of fact ... must not be set aside unless clearly erroneous."

The question presented is as follows:

Whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel explicitly did in this case), or only for clear error, as Rule 52(a) requires.

PARTIES TO THE PROCEEDING

Petitioners (collectively referred to as "Teva") are Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. All were plaintiffs-appellees below.

Respondents are Sandoz Inc., Momenta Pharmaceuticals Inc. (together "Sandoz"), Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (together "Mylan"). All were defendants-appellants below.

Sandoz International GmbH and Novartis AG were defendants in the district court, but were not parties in the court of appeals.

RULE 29.6 STATEMENT

The parent companies of Teva Pharmaceuticals USA, Inc. are: Orvet UK Unlimited, Teva Pharmaceutical Holdings Cooperative U.A., Ivax LLC (f/k/a IVAX Corporation), Teva Pharmaceuticals Europe, B.V., and Teva Pharmaceutical Industries Ltd.; Teva Pharmaceutical Industries Ltd. is the only publicly traded company that owns 10% or more of Teva Pharmaceuticals USA, Inc.

Teva Pharmaceutical Industries Ltd. has no parent company, and no publicly traded company owns 10% or more of Teva Pharmaceutical Industries Ltd.

The parent companies of Teva Neuroscience, Inc. are: IVAX Corporation, Teva Pharmaceuticals USA, Inc., Orvet UK Unlimited, Teva Pharmaceutical Holdings Cooperative U.A., Ivax LLC (f/k/a IVAX Corporation), Teva Pharmaceuticals Europe, B.V.,

and Teva Pharmaceutical Industries Ltd.; Teva Pharmaceutical Industries Ltd. is the only publicly traded company that owns 10% or more of Teva Neuroscience, Inc.

Yeda Research and Development Co. Ltd. is wholly owned by Yeda Trust; no publicly traded company owns 10% or more of Yeda Research and Development Co. Ltd.

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BRIEF FOR PETITIONERS

The interpretation of a term in a patent claim can make the difference between finding the claim valid or invalid, infringed or not infringed. This Court assigned the task of interpreting patents to district courts, not to juries, in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996). As a result, district courts in patent litigation often hold a "*Markman* hearing" to determine the scope of the patent's claims. These hearings may be "live hearings with argument and testimony, sometimes covering several days."[1] The parties identify which terms of the patent claims have a disputed meaning, and both sides offer their proposed constructions, generally supported by the patent's written description, its prosecution history, and evidence of how a person of skill in the art would have understood the disputed terms at the time of the patent application. The district court then resolves that dispute, often making express findings of fact. The parties then litigate infringement and validity in accordance with that claim construction.

But once the case is appealed, the Federal Circuit jettisons all of the district court's work resolving the disputed scientific facts and starts over. Even though Federal Rule of Civil Procedure 52(a)(6) requires all courts of appeals—including the Federal Circuit—to review district courts' factfinding deferentially, the Federal Circuit instead reviews *de novo* "any allegedly fact-based questions relating to claim

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[1] *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 659 F.3d 1369, 1374 (Fed. Cir. 2011) (O'Malley, J., dissenting from denial of rehearing en banc).

construction." *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). As determined dissenters from that misguided rule have pointed out for nearly twenty years, patents are written to be read by skilled artisans, not by lawyers, and factfinding is often necessary to determine the accepted scientific meaning of particular terms or the baseline scientific understanding against which a patent must be read. The Federal Circuit does not disagree that fact evidence often is necessary to claim interpretation; it merely prefers to find the facts for itself, unconstrained by the district court's findings. That is precisely what Rule 52(a)(6) forbids.

This Court should reverse the Federal Circuit's decision and hold that factual findings made during claim construction—like all other factual findings—must be reviewed deferentially on appeal.

OPINIONS BELOW

The decision of the court of appeals (Pet. App. 1a-25a) is reported at 723 F.3d 1363. The district court's claim-construction decision (Pet. App. 26a-72a) is reported at 810 F Supp. 2d 578. A previous decision of the district court denying Sandoz's motion for summary judgment (J.A. 426a-38a) is reported at 749 F Supp. 2d 130. The district court's post-trial findings of fact and conclusions of law (J.A. 848a-1113a) are reported at 876 F. Supp. 2d 295.

JURISDICTION

The judgment of the court of appeals was entered on July 26, 2013. Pet. App. 2a. A petition for rehearing was denied on October 18, 2013. *Id.* at 84a-85a. The petition for a writ of certiorari was filed on Jan-

uary 16, 2014, and granted on March 31, 2014. The jurisdiction of this Court rests on 28 U.S.C. § 1254(1).

STATUTORY PROVISION INVOLVED

Rule 52(a) of the Federal Rules of Civil Procedure provides in pertinent part:

Findings and conclusions by the court; judgment on partial findings

(a) FINDINGS AND CONCLUSIONS.

* * * *

(6) *Setting Aside the Findings.* Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility.

The remainder of Rule 52 and pertinent provisions of the Patent Act are reproduced in the appendix to this brief.

STATEMENT

A. The District Court Concluded, Based On Factual Findings, That Teva's Patent Has A Definite Meaning

Teva is a pharmaceutical company that markets Copaxone®, the leading prescription drug for the treatment of multiple sclerosis. Respondents are generic drug companies that sought FDA approval to market generic formulations of Copaxone®. Teva brought patent-infringement actions, later consolidated, against respondents in the Southern District of New York, contending that respondents' generic

products would infringe various patents held by Teva.

The only claim now at issue is the single claim of U.S. Patent No. 5,800,808. Contrary to the Federal Circuit's incorrect statement (Pet. App. 24a n.5), the '808 patent expires in September 2015. *See id.* at 80a-81a. The other claims previously at issue all expired on May 24, 2014.[2]

1. The Key Term Is "Average Molecular Weight"

The active ingredient in Copaxone®, referred to as "copolymer-1," is a mixture of many polypeptide molecules. Each molecule consists of a chain of four amino acids linked in essentially random sequence but in specified proportions. The chains vary in length and amino-acid sequence, and therefore in molecular weight. The '808 patent and the other patents previously at issue all reflect the inventors' discovery that, contrary to the prevailing understanding at the time, copolymer-1 promised therapeutic effectiveness against multiple sclerosis with an improved side-effect profile when the mixture contained polypeptide molecules of relatively *low* molecular weight.

The patent therefore claims copolymer-1 with particular molecular-weight characteristics. J.A. 1145a (patented method "result[s] in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons").[3] It is undisputed that the claim term "molecular weight"

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[2] This brief therefore refers only to the '808 patent ("the patent") and omits reference to the other similarly worded claims in what the Federal Circuit called "Group I."

[3] A dalton (Da) is a unit of molecular weight, roughly the weight of one proton. A kilodalton (kDa) is 1000 daltons.

in the context of a mixture like copolymer-1 refers to *average* molecular weight. *See, e.g.*, Pet. App. 41a, 62a n.10. The key question in the courts below was whether "average molecular weight" was indefinite as used in the patent.

2. Relying On Expert Testimony, The District Court Found That "Average Molecular Weight" Was Not Indefinite Because Skilled Artisans Would Have Understood Its Meaning

The district court engaged in extensive factfinding about the science reflected in the patent and prosecution history. The court of appeals later reached its own conclusion about these facts without giving any deference to those findings.

Respondents contended that "average molecular weight" had multiple potential meanings and rendered the patent invalid for "indefiniteness"—failure to satisfy the Patent Act's requirement that a claim be definite enough to be understood by a person skilled in the art. *See* 35 U.S.C. § 112 ¶ 2 (2006); *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).[4] The burden to show indefiniteness, by clear and convincing evidence, fell on respondents. *See Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238 (2011).

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[4] Congress amended Section 112 in 2011 in ways not material here. The amendments do not apply to this case, which involves patents filed before September 16, 2012. *See* 35 U.S.C. § 112 note (Supp. V 2011). References in this brief to Title 35 are to the pre-2011 version.

At the time of the invention, the term "average molecular weight," in isolation, had several potential meanings to a person skilled in the art. *See* Pet. App. 4a-5a, 41a. The three meanings relevant here are:

- Peak average molecular weight (M_p);
- Weight average molecular weight (M_w); and
- Number average molecular weight (M_n).

Because the patent did not expressly specify one of those measures, respondents contended that a person of ordinary skill in the art could not have discerned which measure the inventors meant. The district court construed the claim and rejected respondents' contention. The court found that skilled artisans would have understood from the technical discussion in the patent specification that the correct measure was *peak* average molecular weight. Pet. App. 40a-62a.

The district court reached that finding after extensive study of the art. As the district court found and respondents' own experts largely agreed, "[t]he level of ordinary skill in the art in this case is very high," requiring both a Ph.D. and extensive experience in polymer synthesis. J.A. 914a-15a. The parties submitted extensive evidence in the form of expert declarations, discovery documents, and deposition testimony. The parties had a chance to cross-examine each other's witnesses at deposition and to submit deposition testimony to the district court to impeach and rebut opposing experts. After considering all the evidence and holding two hearings, J.A. 20a, 29a, the district court found critically important, and credited, the extensive evidence provided by Teva's expert

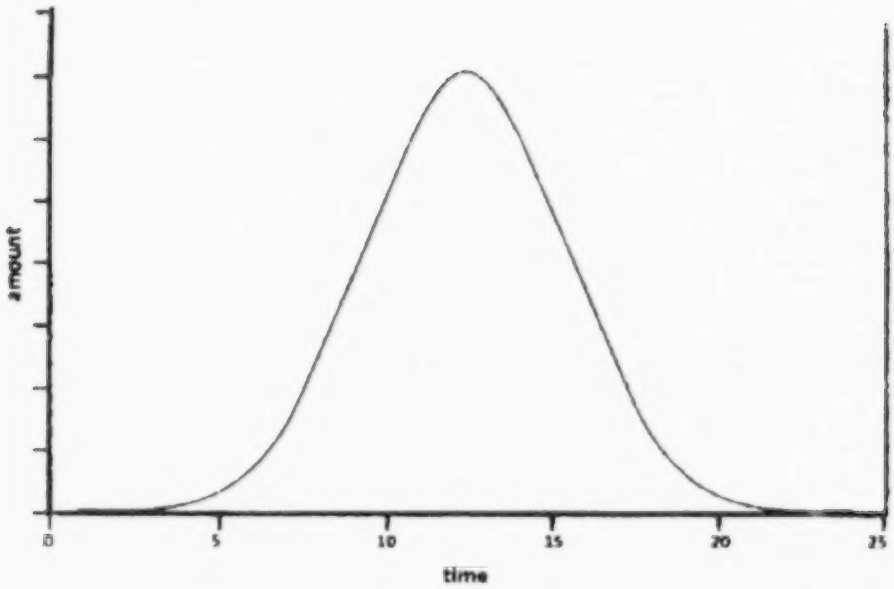
witness, Dr. Gregory Grant. *See* Pet. App. 42a-45a, 48a-50a, 52a.

a. Use of SEC technology: While the patent did not expressly use the term "peak average molecular weight," it did indicate that the average molecular weight should be determined using an analytical technique called size exclusion chromatography ("SEC"). Pet. App. 42a-43a, 144a; J.A. 1143a-44a. Dr. Grant explained that the patent's instruction to determine the average molecular weight using SEC technology would have indicated to a skilled artisan that the intended measure was *peak* average, the only measure that can be read directly from an SEC chromatogram. Pet. App. 125a; J.A. 348a.

SEC technology separates molecules in a sample on the basis of their size, by passing the sample through a column filled with gel particles. Smaller molecules travel through the column more slowly than larger molecules, and molecules of the same size (which generally have the same molecular weight) exit the column at the same time. The user can determine the molecular weight distribution of molecules in the sample by measuring the amount of the sample coming out of the column over time; plotting those amounts against time to produce a graph known as a "chromatogram"; and then calibrating the column to ascertain what molecular weight corresponds to each time. Pet. App. 107a-11a.

The highest point on the chromatogram is the "peak":

Chromatogram



J.A. 809a. The molecular weight that is associated with the peak is the peak average molecular weight—the molecular weight of the molecules present in the sample in greatest abundance. Pet. App. 43a; J.A. 907a, 909a.

Peak average is the *only* expression of average molecular weight that can be derived directly from the chromatogram. Determining either number average or weight average molecular weight, by contrast, requires additional calculations based on the underlying chromatographic data. The patent does not specify any such further calculations. Pet. App. 125a. Furthermore, number average and weight average are generally reported together; it would be uncommon for either to be listed by itself. *Id.* at 129a. Therefore, Dr. Grant testified, a person of ordinary skill in the art would conclude that "average molecular weight" means peak average where it is reported as a single value, obtained using SEC technology, without additional calculations. *Id.* at 125a.

The district court credited Dr. Grant's testimony on this point, which was unrebutted, and found that once a skilled artisan learned that "average molecular weight" would be determined using SEC, "the presumed meaning" of "average molecular weight" to that skilled artisan would have been *peak* average. Pet. App. 43a; *see also* J.A. 437a.

b. The peak of Figure 1: Respondents also asserted that Figure 1 of the patent demonstrated that average molecular weight could not mean peak average. Figure 1 is not a chromatogram, but it plots the results of chromatography experiments.

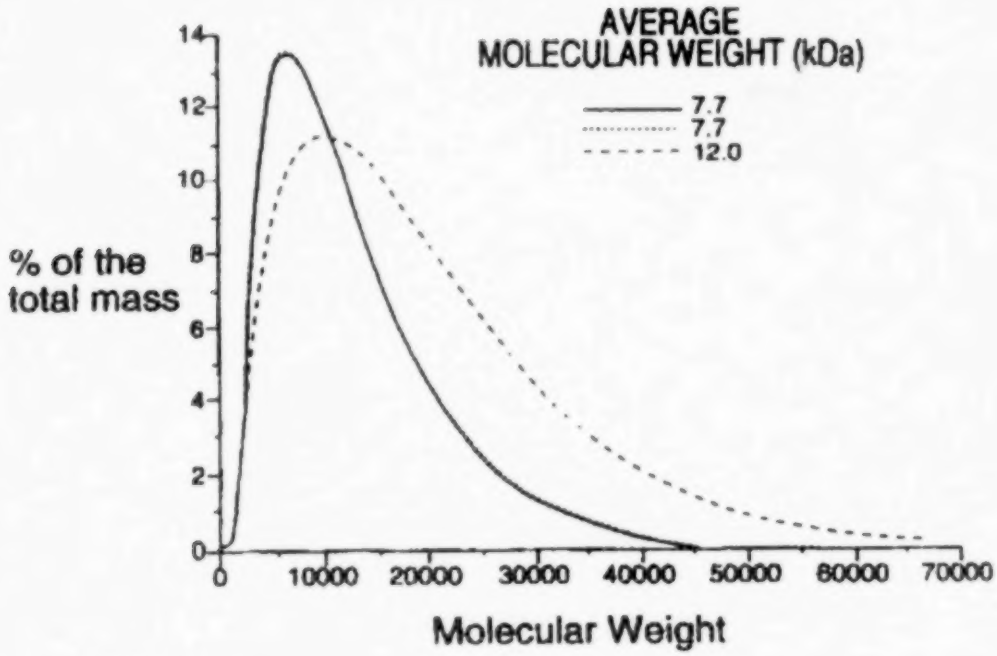


FIG. 1

Pet. App. 139a; J.A. 1141a.

According to the legend, the first two curves (which overlap) were generated from samples having an average molecular weight of 7.7 kDa. Respondents observed that the peak of these curves was not at 7.7 kDa (7700 Da on the x-axis of the figure).

On this point there was a scientific disagreement between Dr. Grant and Mylan's expert, Dr. Ryu. Dr. Grant explained that, because Figure 1 plainly is not a chromatogram and the data from a chromatogram must be transformed to produce Figure 1, a person skilled in the art would not have expected the peak of the curve in Figure 1 to match peak average molecular weight precisely. Rather, a skilled artisan would have understood why the peak value from the chromatogram would shift somewhat during the transformation to Figure 1. Pet. App. 111a-18a, 126a-27a; J.A. 348a-49a, 1119a-20a. Dr. Ryu disagreed and contended that the peak would not be expected to shift. J.A. 375a-76a.

The district court resolved this factual dispute in Teva's favor. The court found that skilled artisans would have understood that Figure 1 was not a chromatogram, but "was created by transforming data from a chromatogram," and that the transformation likely would cause the peaks to shift slightly. Pet. App. 45a, 49a. As a result, the court found, "the fact that the peaks in Figure 1 do not match the listed [average molecular weights (AMWs)] precisely" does not render Figure 1 inconsistent with the use of *peak* average molecular weight. *Id.* at 49a.

c. Prosecution history: There was no pertinent prosecution history on the '808 patent, which issued in 1998. Pet. App. 137a; J.A. 1138a. But on two instances after the '808 patent issued, during prosecution of two of the *other* patents-in-suit, the patent examiner inquired about the meaning of average molecular weight.

In June 2002, during prosecution of the '847 patent, Teva gave a scientifically incorrect response—

that the claim's expression of average molecular weight in kilodalton units "implies a weight average molecular weight." J.A. 1322a. In fact, as both sides' experts agreed, the use of kilodaltons does *not* distinguish the type of average molecular weight: *all* methods of expressing molecular weight use kilodalton units. Pet. App. 128-29a.

Later, in December 2004, during prosecution of the '539 patent, the same primary examiner who examined all three patents[5] again raised the same issue. J.A. 1343a, 1345a. Teva responded that the patent specification (including Figure 1) would make clear to a skilled artisan that average molecular weight is *peak* average. J.A. 1355a. The Patent and Trademark Office (PTO) accepted the changed answer.

Because both sides' experts agreed that the earlier of the two statements was scientifically flawed, Pet. App. 52a, the district court found as a fact that a person of ordinary skill in the art would not credit the earlier statement. The later statement, by contrast, was consistent with the specification and helped to defeat respondents' indefiniteness claim. *Id.* at 45a, 52a.

At trial, respondents pursued a different indefiniteness theory and proffered no additional evidence on the meaning of "average molecular weight." The district court found that respondents had failed to prove their indefiniteness defense by clear and convincing evidence. J.A. 1066a-69a. The court then entered judgment that the patents were not invalid. Pet. App. 76a-78a. The district court also held that Teva had proved infringement, and enjoined re-

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[5] *See* J.A. 1138a, 1188a, 1233a (Examiner Krass).

spondents from committing any act of infringement during the remaining life of the patents. *Id.* at 76a-81a.

B. The Federal Circuit Reviewed The Evidence *De Novo* And Found The Patent Indefinite.

On appeal, respondents made no attempt to argue that the District Court clearly erred in any of these findings. Rather, they asked the Federal Circuit to consider *de novo* whether the patent claim was indefinite, in line with the circuit's precedent that even "any allegedly fact-based questions relating to claim construction" are reviewed "*de novo* on appeal." *Cybor*, 138 F.3d at 1456.

The court of appeals reversed the district court and held the patent invalid because the term "average molecular weight" was indefinite. Pet. App. 1a-11a.[6] The court expressly stated that it would review "*de novo*" and would not defer to the district court's factual findings. *Id.* at 7a, 10a. The court concluded that a person of ordinary skill would *not* be able to discern the meaning of "average molecular weight" as used in the patent. *Id.* at 8a-11a.

Although both Dr. Grant and the district court had addressed every one of the grounds on which the panel disagreed with the district court's reading of the patent, the panel gave no weight to the district court's contrary factual findings.

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[6] The court of appeals affirmed the infringement finding and the ruling that the remaining claims were not invalid. *See* Pet. App. 12a-24a.

- *SEC technology:* The panel emphasized that other measures of average molecular weight—number average and weight average—"can also be obtained from the data generated by the SEC method after some calculations." Pet. App. 10a. But the panel did not refute or even acknowledge the key factual and scientific bases for the district court's contrary finding—that peak average would be the "presumed meaning" to a skilled artisan, in part because peak average was the only measure that could be read directly from a chromatogram "*without* any 'further calculation'" and the patent disclosed no further calculations. *Id.* at 43a, 48a (emphasis added).

- *Figure 1:* The panel found significant that the peak of the curve in Figure 1 was not at 7.7 kDa, the specified "average molecular weight." *Id.* at 10a-11a. The panel equated the peak of that curve with the sample's peak average molecular weight. *See id.* at 10a. But the panel did not refute or even acknowledge the District Court's factual findings, based on Dr. Grant's testimony: that peak average is found from a chromatogram; that Figure 1 is not a chromatogram; and that the peak would be expected to shift when the data was converted from a chromatogram to Figure 1. *Id.* at 45a-49a.

- *Prosecution history:* The panel emphasized that the two statements in the subsequent patents' prosecution history were inconsistent with each other. *Id.* at 9a. But the panel did not refute or even acknowledge the District Court's factual finding—based on undisputed evidence—that

any skilled artisan would recognize the error in the earlier statement and therefore would not rely on it. *Id.* at 52a.

The Federal Circuit then denied rehearing and issued its mandate. Pet. App. 84a-85a.[7]

SUMMARY OF ARGUMENT

The Federal Circuit has asserted the power to reweigh or even find facts on appeal by engaging in *de novo* review. But under Federal Rule of Civil Procedure 52(a)(6), *de novo* review and factual findings are incompatible. When patent claim construction entails factfinding—as it did here, and as it often does—then the Federal Circuit is limited to reviewing those findings for clear error.

I. Factfinding takes place in the district court, not the court of appeals. A court of appeals is not permitted to weigh the facts for itself or to find new facts. Findings of fact may not be set aside "unless clearly erroneous." Fed. R. Civ. P. 52(a)(6). That rule of deference "does not make exceptions." *Pullman-Standard v. Swint*, 456 U.S. 273, 287 (1982).

District courts have more expertise with factfinding, and tools that appellate judges lack (such as the

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[7] Since the panel's decision, Teva and respondents have separately engaged in various proceedings before the Patent and Trademark Office. Teva asked the PTO to reissue the '808 patent with the perceived indefiniteness corrected. *See* Cert. Reply 5 n.3; 35 U.S.C. § 251. The PTO denied the request on grounds not relevant here. Teva's notice of appeal of that decision to the Patent Trial and Appeal Board is due July 3, 2014. More recently, one of the respondents asked the PTO to initiate an *ex parte* re-examination of the '808 patent (Control No. 90/013,249), again on grounds not relevant here.

ability to appoint their own experts or to question the parties' experts directly and personally). Those considerations led this Court to promulgate Rule 52(a)(6): the Court determined that district courts are better at factfinding—in *all* cases, not just those involving live testimony and credibility assessment. And even if district courts lacked those advantages, appellate factfinding would still be unjustifiable because of the systemic costs. *De novo* review of factual findings would "contribute only negligibly to the accuracy" of those findings, yet impose "a huge cost in diversion of judicial resources." *E.g.*, *Anderson v. City of Bessemer City*, 470 U.S. 564, 574-75 (1985).

II. Construing a patent does not necessarily present a pure question of law, chiefly because patents are written for scientists, not lawyers. *Nautilus*, 134 S. Ct. at 2128. A court often cannot interpret a patent without first understanding what skilled people in the relevant art knew, and what words they used, when the patent application was filed. To gain that understanding, the district court frequently must resolve conflicting accounts of historic and scientific fact. Long before the Federal Circuit was created, federal appellate courts understood that these endeavors by district judges were *factual* inquiries squarely governed by Rule 52.

The Federal Circuit originally did not dispute that district courts' work involves factfinding. Instead, it just asserted the power to review all aspects of claim construction *de novo*, including the "allegedly fact-based" ones. *Cybor*, 138 F.3d at 1456. That holding is flatly incompatible with Rule 52(a)(6). Later, the Federal Circuit changed tacks and stated boldly that there *is* no factfinding during claim construction.

E.g., *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1284-85, 1289 (Fed. Cir. 2014) (en banc).[8] That assertion is equally unavailing. The Federal Circuit has itself held, correctly, that evidence from outside the patent will often be needed to understand the patent. And when district courts follow the Federal Circuit's direction, take evidence, and resolve evidentiary disputes, they are obviously engaged in factfinding—just as they are when taking extrinsic evidence about usage of trade in a contract or tariff case. *See, e.g.*, *Great N. Ry. Co. v. Merchants' Elevator Co.*, 259 U.S. 285, 293 (1922). The ultimate question may be a legal one, but the subsidiary questions are factual in nature. *Cf., e.g.*, *Ornelas v. United States*, 517 U.S. 690, 699-700 (2006) (probable cause is a question of law that rests on subsidiary questions of fact). Rule 52(a)(6) mandates deference to the district court's answers to those factual questions.

III. Ultimately the Federal Circuit's adoption of *de novo* review reflects its belief that more searching appellate review will promote a desirable "uniformity" in claim construction. Even if that policy judgment could overcome Rule 52(a)(6)'s plain language, two decades' experience shows that *de novo* review of all aspects of claim construction does more harm than good. It contributes to instability and prolonged delays in patent litigation. District courts' findings are not respected on appeal, which affects litigants' choices (more of them appeal, making litigation longer and more costly) and also district judges' choices (some have given up writing reasoned claim-construction decisions). If district judges

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[8] *Lighting Ballast* is reprinted at Cert. Reply App. 1a-95a.

sometimes resolve the facts of particular cases differently than the Federal Circuit would, that is not a problem to be solved through heightened appellate review. It is simply the consequence of our litigation system, in which *trial*, not appeal, is the "main event." *Anderson*, 470 U.S. at 575 (citation omitted).

IV This case illustrates the flaws in *de novo* review. The District Court took more than a year to absorb the relevant facts in this highly complex area, one in which the level of ordinary skill requires a Ph.D. and more. The court found as a matter of fact, after a lengthy *Markman* process, that a person of ordinary skill in the art could understand Teva's patent. On key factual points it credited Teva's expert over respondents'. The Federal Circuit completely undid that work in four short paragraphs (Pet. App. 8a-10a), crediting its own lay understanding of scientific matters set out in the patent specification and prosecution history. And that lay understanding was wrong. The Federal Circuit did not even acknowledge the findings that refuted its position, much less identify any reversible clear error.

Scientific misunderstandings like this one are the natural consequence of the Federal Circuit's no-deference rule. The Federal Circuit has become so accustomed to finding its own facts that it scarcely takes note of the findings below. Here, in substance, the Federal Circuit credited respondents' expert submission over Teva's. But Rule 52(a)(6) "plainly does not entitle a reviewing court to reverse the finding of the trier of fact simply because it is convinced that it would have decided the case differently." *Anderson*, 470 U.S. at 573. Because that is precisely

what the Federal Circuit did, this Court should reverse.

ARGUMENT

The rule in the Federal Circuit is that every aspect of claim construction, even "allegedly fact-based questions," is reviewed *de novo*. *Cybor*, 138 F.3d at 1456. The Federal Circuit recently reaffirmed that approach by a divided vote of 6-4, conspicuously not defending its approach on the legal merits but relying instead on *stare decisis*. *Lighting Ballast*, 744 F.3d at 1284 (refusing to allow the standard of review to depend on "whether there was or was not a fact at issue"). On the legal merits, the Federal Circuit's rule cannot stand. Resolving matters of historical fact, such as the knowledge or ordinary practice in a given art, is factfinding. And under Rule 52(a)(6), appellate review of factfinding is limited: findings must be sustained unless clearly erroneous. The Federal Circuit cannot dodge that rule by calling a factual question a legal one.

I. The Federal Rules Of Civil Procedure Preclude Appellate Courts From Second-Guessing District Courts' Factual Findings.

Every circuit, including the Federal Circuit, is bound by Rule 52(a)(6). Every circuit, including the Federal Circuit, is precluded by that Rule from reversing factual findings—*any* factual findings—unless those findings are clearly erroneous. *See, e.g.*, *Highmark Inc. v. Allcare Health Mgmt. Sys., Inc.*, 134 S. Ct. 1744, 1748 (2014) (reaffirming, in a case from the Federal Circuit, that "decisions on 'questions of fact' are 'reviewable for clear error'") (citation

omitted). That Rule reflects this Court's longtime recognition that the district courts are better suited to finding facts.

A. District Courts Have Responsibility For Factfinding

Congress and this Court have given responsibility and resources for factfinding to the district courts. District-court proceedings provide better tools for adversarial testing of factual assertions than appellate briefs and argument do. And having facts largely settled in the district court—subject only to deferential review—promotes efficiency, finality, and respect for the judiciary.

For those reasons, Rule 52(a)(6) unambiguously limits the power of the federal appellate courts: in matters tried to a district court, the court's "[f]indings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous." Fed. R. Civ. P. 52(a)(6). That rule "does not make exceptions." *Pullman-Standard*, 456 U.S. at 287. It applies to "*all* actions tried upon the facts without a jury." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 394-95 (1948) (emphasis added). And in all such actions, it is the appellate court's "*obligation* ... to accept a district court's [factual] findings unless clearly erroneous." *Pullman-Standard*, 456 U.S. at 287 (emphasis added).

The obligation to review facts deferentially does not evaporate just because the factfinding lays the groundwork for a legal conclusion that the appellate court will review *de novo*. Rule 52(a)(6) "does not divide findings of fact into those that deal with 'ultimate' and those that deal with 'subsidiary' facts."

Pullman-Standard, 456 U.S. at 287.[9] Thus, for example, a district court's conclusion that a search or seizure was supported by probable cause is reviewed *de novo*. *Ornelas*, 517 U.S. at 699. But the district court's underlying findings of fact—which may include findings about the inferences a police officer draws in light of his training or experience, or the practices and characteristics of criminal organizations—are reviewed deferentially, for clear error. *Id.* at 699-700.[10] The Court has reiterated that point several times since *Ornelas*—holding that a given conclusion may be subject to *de novo* review, but that the supporting facts must be reviewed only for clear error. *United States v. Bajakajian*, 524 U.S. 321, 336 n.10 (1998) (excessiveness of a fine); *Cooper Indus., Inc. v. Leatherman Tool Grp., Inc.*, 532 U.S. 424, 440 & n.14 (2001) (excessiveness of a punitive-damages award); *Knowles v. Mirzayance*, 556 U.S. 111, 126 (2009) (ineffective assistance of counsel).

This Court opted for deferential review of factfinding for several reasons—the most important of which is that "[t]he trial judge's major role is the determination of fact, and with experience in fulfilling that role comes expertise." *Anderson*, 470 U.S. at 574. District courts see the weaknesses of each party's

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[9] This Court has held that in a narrow category of cases, the Constitution requires independent, searching appellate assessment of certain issues significant to protected rights, such as whether a defamatory statement was made with actual malice. Rule 52(a) does not fully apply to those cases. *Bose Corp. v. Consumers Union of United States, Inc.*, 466 U.S. 485, 514 & n.31 (1984). No such constitutionally-compelled exception is at issue here.

[10] *Ornelas* was a criminal case, but the same clear-error standard applies. *Maine v. Taylor*, 477 U.S. 131, 145 (1986).

case exposed through adversarial testing. They acquire a "full knowledge of the [case's] factual setting" that is difficult for an appellate court to match. *Pierce v. Underwood*, 487 U.S. 552, 560 (1988). And armed with that knowledge, they are in "a superior position to appraise and weigh the evidence." *Zenith Radio Corp. v. Hazeltine Research, Inc.*, 395 U.S. 100, 123 (1969); *see, e.g.*, *Brown v. Plata*, 131 S. Ct. 1910, 1945 (2011) ("The adversary system afford[s] the [district] court an opportunity to weigh and evaluate evidence presented by the parties."). In short, the "first-instance decisionmaker[]" has a superior "'feel' for the overall case." *Weisgram v. Marley Co.*, 528 U.S. 440, 443 (2000) (citation omitted).

Allowing litigants to relitigate the facts on appeal would also run contrary to basic principles of "stability and judicial economy." Fed. R. Civ. P 52 advisory committee's note (1985). "Duplication of the trial judge's efforts in the court of appeals would very likely contribute only negligibly to the accuracy of fact determination," yet retrying the facts on appeal would come "at a huge cost in diversion of judicial resources." *Anderson*, 470 U.S. at 574-75. "[T]he parties to a case on appeal have already been forced to concentrate their energies and resources on persuading the trial judge that their account of the facts is the correct one; requiring them to persuade three more judges at the appellate level is requiring too much." *Id.* at 575.

Just as importantly, the principle of deference protects the very "legitimacy of the district courts in the eyes of litigants." Fed. R. Civ. P. 52 advisory committee's note (1985). Telling the parties that anything that happens in district court can be litigated

over again on appeal would "impair[] confidence in the trial courts," 9C Charles Alan Wright & Arthur R. Miller, *Federal Practice & Procedure* § 2587, at 439 (3d ed. 2008), and improperly shift parties' focus from the trial to the appeal. As this Court has said, "the trial on the merits should be 'the "main event" ... rather than a "tryout on the road." '" *Anderson*, 470 U.S. at 575 (quoting *Wainwright v. Sykes*, 433 U.S. 72, 90 (1977)).

B. District Courts' Role Extends Beyond Resolving Credibility Disputes

Because district courts are better positioned to learn and master the record, their factfinding role extends beyond just acting as lie detectors during live testimony. District judges have primary responsibility for *the facts*, not just for *the witnesses*. Accordingly, the Federal Rules and the decisions of this Court have long made clear that federal district courts are entitled to deference in *all* their "[f]indings of fact, whether based on oral or other evidence." Fed. R. Civ. P. 52(a)(6). Findings based on "physical or documentary evidence or inferences from other facts" reflect the district court's familiarity with the overall case, just as findings based on live testimony do, and likewise receive deference on appeal. *Anderson*, 470 U.S. at 574; *accord U.S. Gypsum*, 333 U.S. at 394 (Rule 52(a)'s clear-error standard governs findings based on "inferences drawn from documents or undisputed facts"); *Commissioner v. Duberstein*, 363 U.S. 278, 291 (1960) (same).

To be sure, findings based on "oral ... evidence," and the credibility of live witnesses, are entitled to

extra deference: "[T]he reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility." Fed. R. Civ. P. 52(a)(6). But that principle does not "alter [the] clear command" of Rule 52(a) that *all* district court findings receive deferential clear-error review. *Anderson*, 470 U.S. at 574.[11]

Rule 52(a)(6) firmly rejects the notion that appellate judges can dispense with deference whenever they deem themselves to be "in as good a position as the trial court" to judge the facts. Fed. R. Civ. P. 52 advisory committee's note (1985). While some judges have been drawn to that notion over the years, *see id.*; *Anderson*, 470 U.S. at 574, it was and is altogether inconsistent with "both the plain meaning and the stated intent of the governing rule," as commentators perceived from the outset. *E.g.*, Charles Alan Wright, *The Doubtful Omniscience of Appellate Courts*, 41 Minn. L. Rev. 751, 770 (1957), *cited in* Fed. R. Civ. P. 52 advisory committee's note (1985). But to eliminate any doubt, this Court amended the Rule in 1985 to explicitly require deference to factual findings "whether based on oral or other evidence." Fed. R. Civ. P. 52(a)(6).

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[11] The same rule applies whether the evidence supporting a finding is contested or uncontested. Indeed, giving less deference to uncontroverted findings would make little sense; in an adversarial process, material facts that are not contested are highly likely to be accurate. Rule 52 accords the same deference on appeal to all findings, "whether the finding is of a fact concerning which there was conflict of testimony, or of a fact deduced or inferred from uncontradicted testimony." Fed. R. Civ. P. 52 advisory committee's note (1937); *accord Duberstein*, 363 U.S. at 291; *U.S. Gypsum*, 333 U.S. at 394.

Under Rule 52, especially since its 1985 amendment, district judges find *all* the facts, not just those turning on witness credibility. And when they exercise that authority, their findings may not be set aside on appeal unless clearly erroneous.

C. District Courts Are Particularly Well Suited To Make Scientific Determinations

The rationale for deference to district court fact-finding is "[p]articularly" strong in scientific or technical contexts. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 610 (1950). When the factual question is a scientific one, "so much depends upon familiarity with specific scientific problems and principles," and the requisite learning is "not usually contained in the general storehouse of knowledge and experience." *Id.* District courts face fewer institutional constraints than appellate courts on the ability to gain that learning over the course of a given litigation: they consider a developing record, rather than a closed one; they have great discretion to hold a longer hearing, or many hearings; and they can interact directly with experts, even questioning them personally.

When the admissibility of scientific evidence is at stake, this Court has repeatedly and firmly expressed confidence in district courts' ability to make the necessary judgments about validity, reliability, and probative value. District courts enjoy "broad latitude" to determine reliability within generous limits. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 142, 152-53 (1999); *see Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 138-39 (1997); *United States v. Scheffer*,

523 U.S. 303, 318 (1998) (Kennedy, J., concurring in part and concurring in the judgment) (noting "the considerable discretion given to the trial court in admitting or excluding scientific evidence"). The same principle applies with equal force when the district court's task involves not just gatekeeping but factfinding.

II. Patent Claim Construction Often Entails Factfinding

Patents are not written primarily to be read by judges or lawyers. *Nautilus*, 134 S. Ct. at 2128. Rather, they are scientific texts designed to be read and used by specialists in the relevant field. Their "descriptions and terms of art often require peculiar knowledge and education to understand them aright," and they often contain slight—but important—"verbal variations, scarcely noticeable to a common reader" but "detect[able] by an expert in the art." *Bischoff v. Wethered*, 76 U.S. 812, 815 (1870). For that reason, judges often need to take factual evidence, such as expert testimony, to enable them to understand patent claims.

Receiving that factual evidence, and resolving disputes between competing experts and other witnesses, is classic factfinding. Determining the common usage in a particular scientific subfield, or ascertaining the effect of converting one type of graph to another, certainly cannot be described as matters of *law*. Nor do these matters of fact lose their factual character merely because they are necessary to patent claim construction. Factual findings must be reviewed deferentially no matter what they are used for—whether determining probable cause, interpret-

ing an ambiguous contract, or construing a patent. *Cf., e.g., Ornelas*, 517 U.S. at 699.

A. Interpreting Patents From The Perspective Of A Skilled Artisan Often Requires Factfinding

Patents are written for a particular audience—skilled artisans—and they are interpreted from the perspective of that audience. Congress has explicitly directed that the patent specification be written for the benefit of a "person skilled in the art." 35 U.S.C. § 112 ¶ 1; *see also id.* § 103(a) (obviousness judged from the perspective of a person skilled in the art). And patents are construed as a whole, meaning that the claims are drafted in light of the specification and the specification informs the meaning of the claims. Because of how patents are written, and for whom, frequently "it is difficult for persons not skilled in the art to ... appreciate the distinctions which may exist in the words of a claim when read in the context of the art itself." *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 233 (1942); *accord Mowry v. Whitney*, 81 U.S. 620, 644 (1872) ("[T]he unskilled may not be able to gather from [the specification] how to use the invention.").

In construing the patent, therefore, a federal judge must replace the perspective she would apply to a statute or a consumer contract with the perspective of a skilled artisan. *See, e.g., United Carbon*, 317 U.S. at 233 (in claim construction, relying on testimony as "the clearest exposition of the significance which the terms employed in the claims had for those skilled in the art"); *Carnegie Steel Co. v. Cambra Iron Co.*, 185 U.S. 403, 437 (1902) ("The specifi-

cation of the patent is not addressed to lawyers, or even to the public generally, but to the manufacturers of steel ....").[12] Doing that requires the court to ascertain facts from outside "the general storehouse of knowledge and experience." *Graver Tank*, 339 U.S. at 610. In this case, for example, there was a wide gap between the layperson and the skilled artisan—a Ph.D. with extensive experience in polymer synthesis. *See* J.A. 914a-15a.

Courts often entertain evidence from outside the patent documents during claim construction. The most straightforward reason to entertain such evidence is to determine the specialized meaning that particular terms have to skilled artisans. *See, e.g., United Carbon*, 317 U.S. at 233-34. The ultimate scope of the patent claims may be a legal question, but (as is common) the answer to that legal question will often depend directly on resolving questions whose answers lie outside the four corners of the patent and its prosecution history: What was the level of ordinary skill in the art at the relevant time? Did the relevant term have a specialized meaning to someone with that level of skill? And if so, what was that meaning? These are factual questions; their answers bear legal significance because of the well-established "heavy presumption" that the meaning of a patent claim term is the meaning that people with

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[12] *See also, e.g., Gen. Elec. Co. v. Wabash Co.*, 304 U.S. 364, 372 (1938) (examining whether claims "conveyed definite meaning to those skilled in the art").

ordinary skill in the art would give it, in the relevant context.[13]

Courts also take extrinsic evidence to aid in understanding the specification and the relevant art more broadly. Understanding the relevant art can help in construing a patent from the perspective of a skilled artisan even when the relevant term does not have a single, well-established meaning. For instance, both this Court and the Federal Circuit have often stated that the written description contained in the patent specification is a valuable (often the most valuable) aid to construing the patent claims.[14] But often the written description—written for skilled artisans, *see* 35 U.S.C. § 112 ¶ 1—needs some elucidation before it can be used by lawyers and judges to interpret the patent claims. Before the court can use the written description for that purpose, its understanding of the written description must be *scientifically and factually* correct.[15]

Expert testimony about the art can also assist in understanding the prosecution history—the back-and-forth between the inventor and the PTO. Prosecution history is prone to ambiguity, *see Phillips*, 415 F.3d at 1317 (citing cases), and may even contain er-

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[13] *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001); *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005).

[14] *E.g., United States v. Adams*, 383 U.S. 39, 48-49 (1966); *Phillips*, 415 F.3d at 1315-17.

[15] *See, e.g., Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1354 (Fed. Cir. 2011) (relying on expert testimony to understand discussion in specification); *see also Phillips*, 415 F.3d at 1318 (explaining that expert testimony can be useful "to provide background on the technology at issue" and "to explain how an invention works").

rors. Moreover, even taken at face value, prosecution history reflects an exchange with an examiner who is a subject-matter expert, and often not an attorney. Thus, like the patent itself, the prosecution history is read from the perspective of a person of ordinary skill in in the art. And as with the patent itself, resolving ambiguities, identifying errors, and simply understanding the terminology and the science may require the assistance of expert evidence. *See, e.g., Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, 508 F.3d 1366, 1373 (Fed. Cir. 2007) (discounting a statement made in prosecution history when a technical witness explained that adhering to that statement would render the invention inoperative).

Finally, in cases where the defense of indefiniteness under 35 U.S.C. § 112 ¶ 2 intersects with claim construction, the dominant inquiry will be a factual one turning on a skilled artisan's knowledge. *See Nautilus*, 134 S. Ct. at 2128. As this Court recently clarified, the question in indefiniteness cases is whether the "claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *Id.* at 2129. For that reason, indefiniteness cases can often turn on a factual examination of whether the standard level of knowledge in the art enables a skilled artisan to understand what is "distinctly claimed" by the patent. *See Carnegie Steel*, 185 U.S. at 437.

Thus, for example, this Court in *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923), relied on expert testimony to sustain a patent against a challenge that the claim terms "substantial

elevation" and "rapidly" were indefinite. Expert testimony showed that these terms were precise enough for a skilled artisan and, indeed, that no greater precision was possible because the exact operating conditions "must be found by practice." 267 F. 847, 854 (D. Me. 1920). And there was ample marketplace evidence that the invention was understood from the patent because it had been quickly and successfully adopted "by the whole trade." 261 U.S. at 66. This Court accordingly concluded that "[t]he *evidence* disclose[d] that [a skilled artisan] had no difficulty" comprehending the claimed invention. *Id.* at 65-66 (emphasis added).

B. A District Court Engages In Factfinding When It Uses Evidence Of Scientific Understanding To Resolve Ambiguities In A Patent

The Federal Circuit has historically taken the view that the distinction between fact and law is so malleable that the Federal Circuit can designate as "legal" any question that it thinks would benefit from *de novo* review.[16] Rule 52(a)(6) is not so easily circumvented.

Rather, Rule 52(a)(6) unambiguously applies if ascertaining the knowledge or vocabulary of skilled artisans, including resolving disputes among experts, amounts to finding facts. Under this Court's cases, plainly it does.

Judge Easterbrook has put the point pithily while sitting by designation to try a patent case: "[J]udges

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[16] *See, e.g.*, *Lighting Ballast*, 744 F.3d at 1289-90 (relying on *Miller v. Fenton*, 474 U.S. 104, 113-14 (1985)).

should not pretend that all nominally 'legal' issues may be resolved without reference to facts.... What seems clear to a judge may read otherwise to a skilled designer. That is why we had a trial." *In re Mahurkar Double Lumen Hemodialysis Catheter Patent Litig.*, 831 F. Supp. 1354, 1359 (N.D. Ill. 1993), *aff'd on other grounds*, 71 F.3d 1573 (Fed. Cir. 1995).

1. Understanding the level of ordinary skill in the art at the relevant time is a "basic factual inquir[y]," as this Court said in *Graham*. Science is not law, and ascertaining what scientists know is not a legal question, but a factual one. *See, e.g.*, *Taylor*, 477 U.S. at 146 ("[T]he more specific question whether scientifically accepted techniques exist for the sampling and inspection of live baitfish is one of fact, and the District Court's finding that such techniques have not been devised cannot be characterized as clearly erroneous.").

Adding the time element—knowledge or usage in the relevant art *at the time the patent application was filed*[17]—makes the inquiry, if anything, even more a question of historical fact. The court asks what a skilled artisan *would have known* at some earlier time, not what she would know today. *Cf. Bose*, 466 U.S. at 498 ("It surely does not stretch the language of the Rule to characterize an inquiry into what a given person knew at a given point in time as a question of 'fact.'"). That requires a court to focus on developments in the art and when they became generally accepted—classic factual inquiries. *Taylor*, 477 U.S. at 146.

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[17] *See Nautilus*, 134 S. Ct. at 2128.

Similarly, vocabulary, usage, and customs among the relevant community are factual questions. For instance, this Court expressly deferred to a district court's resolution of the question whether "custom or practice in the international banking community" could be the basis for inferring an agreement among the parties. *Citibank, N.A. v. Wells Fargo Asia Ltd.*, 495 U.S. 660, 671-72 (1990). The existence of a "relevant custom or practice" was a factual matter on which Rule 52(a) required deference to the district court's finding. *Id.*

2. Ascertaining historical facts, such as the knowledge of a skilled artisan at a particular time, does not become a legal inquiry simply because those facts, once found, will be used to illuminate a legal document or answer another legal question. While the ultimate interpretation of a legal document is indeed a legal question, interpretation has various ingredients, and some of those ingredients—*e.g.*, "what words appear in the contract?" or "do those words have a specialized meaning?"—are factual.

As this Court has explained in the context of other legal documents: the question "whether words in the [document] were used in their ordinary meaning, or in a peculiar meaning" specific to a particular business, is "obviously" a question "of fact" rather than of interpretation. *Great N. Ry.*, 259 U.S. at 293 (interpreting a railroad tariff). Indeed, the interpretation of a legal document can turn completely on a factual question: whether a single word has a specialized meaning in the industry, or instead just carries its ordinary dictionary meaning. *E.g.*, *Tex. & Pac. Ry. v. Am. Tie & Timber Co.*, 234 U.S. 138, 146-47 (1914) (construction of a tariff depended entirely on the fac-

tual question whether the term "lumber" included railway crossties in the usage of the relevant business); *see Great N. Ry.*, 259 U.S. at 293.[18]

The same rule is widely followed in contract interpretation. An interpretive question is a question of fact "if it depends on the credibility of extrinsic evidence or on a choice among reasonable inferences to be drawn from extrinsic evidence." *Restatement (Second) of Contracts* § 212(2) & cmt.e (1981); *accord, e.g.*, 5 Margaret N. Kniffin, *Corbin on Contracts* § 24.30, at 332-37 (rev. ed. 1998); *Rankin v. Fidelity Ins. Trust & Safe Deposit Co.*, 189 U.S. 242, 252-53 (1903); *Meyers v. Selznick Co.*, 373 F.2d 218, 221-23 (2d Cir. 1966) (Friendly, J.). Similarly, the meaning of the contract itself necessarily depends on extrinsic evidence—and on factfinding—when the interpretive question turns on what the usage or custom was in a given industry at a particular time. Accordingly, "the existence of a particular custom or usage" is a question of fact. 12 Richard A. Lord, *Williston on Contracts* § 34:19, at 174-78 (4th ed. 2012); *accord, e.g., Restatement, supra*, § 222(2).

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[18] Similarly, this Court has acknowledged that where parol evidence is admissible to aid in interpreting a land patent, it can create a factual question. *Brown v. Huger*, 62 U.S. 305, 320-21 (1859) ("In cases of boundary which depend upon the swearing of witnesses," it is the factfinder that makes "a decision upon the weight of the testimony and the facts which the testimony conduces to establish.") (quoting *Cockrell v. M'Quinn*, 20 Ky. (4 T.B. Mon.) 61, 62, 1827 WL 2577, at *2 (1826)); *see also Ott v. Soulard*, 9 Mo. 581, 1845 WL 3798, at *15-16 (1845) (following *Cockrell* in a land-patent case and holding that parol evidence, including "usage and custom," presented a factual component to be resolved by the factfinder).

C. Patent Law Already Treats Closely Related Questions As Factual

The Federal Circuit's no-deference rule for claim construction leads to a puzzling disuniformity in patent doctrine. The *same evidence* can give rise to factual issues for purposes of other patent-law questions that the district court must answer, but be treated as purely legal by the Federal Circuit when it informs claim construction. As shown above, merely touching on the interpretation of a legal document does not turn a factual determination into a legal one.

For instance, prior art is often relevant to claim construction.[19] Yet in other patent-related contexts, this Court has made clear that the "scope and content" of the prior art is a factual question. *Graham*, 383 U.S. at 17. So is the comparison of the prior art with the patented invention. *See id.*; *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 280 (1976). And while the defense of obviousness presents ultimately a legal question, it "lends itself to [these] basic *factual* inquiries." *Graham*, 383 U.S. at 17 (emphasis added). In fact, in some cases the district court's factfinding will all but compel the outcome of the legal inquiry. *E.g.*, *Sakraida*, 425 U.S. at 280.

This Court has also described as "factual" the application of the doctrine of equivalents to determine what is covered by a patent in addition to what is explicitly described in the claims—*i.e.*, what is "equiva-

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[19] *See, e.g.*, *Harris Corp. v. IXYS Corp.*, 114 F.3d 1149, 1153 (Fed. Cir. 1997) (prior art "render[ed] [one] proposed construction ... much less plausible" because "claims should be read in a way that avoids ensnaring prior art").

lent" to what is claimed. *See Graver Tank*, 339 U.S. at 609 ("A finding of equivalence is a determination of fact."); *see also Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 37-39 (1997) (reserving the judge/jury question). "An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was." *Graver Tank*, 339 U.S. at 609. Thus, this Court has characterized as "factual" an inquiry that bears a strong resemblance to claim construction—a determination of what a person of ordinary skill in the art would consider "equivalent" to the invention described in the patent claim.

Similarly, the background knowledge of a skilled artisan is treated as an evidentiary issue in ascertaining "enablement" (whether the specification enables a skilled artisan to practice the patent, 35 U.S.C. § 112 ¶ 1). *E.g.*, *Loom Co. v. Higgins*, 105 U.S. 580, 586 (1882) ("[A]s it cannot be expected that the court will possess the requisite knowledge for this purpose, it becomes necessary that it should avail itself of the light furnished by the evidence to enable it to understand the terms used in the patent ...."). But for claim-construction purposes the Federal Circuit treats that same background knowledge as a question of law—a further illustration of why insisting on *de novo* review requires the court to treat factual issues as legal ones.

III. The Federal Circuit's Various Rationales For Reviewing Factual Findings *De Novo* Are Unpersuasive

Factual findings are reviewed only for clear error, and the factual findings that underlie claim construction are no different than factual findings in any other context. That answers the question presented. Rule 52(a)(6) does not allow the Federal Circuit to select whatever standard of review it thinks best. Just as this Court disapproved the Federal Circuit's attempt to review *agency* factfinding by a standard less deferential than the one Congress prescribed in the Administrative Procedure Act, *Dickinson v. Zurko*, 527 U.S. 150, 162, 165 (1999), this Court should disapprove the Federal Circuit's attempt to review *district court* factfinding by a standard less deferential than Rule 52's. As in *Zurko*, there is no warrant for a Federal Circuit-only standard.

The Federal Circuit does not dispute the propriety of using extrinsic evidence in claim construction. The problem is that the Federal Circuit, preferring to weigh that evidence for itself without deferring to the district court, denies that there is anything factual to be drawn from that evidence. In adopting its no-deference rule, the Federal Circuit refused to acknowledge that even "resolving disputes" within the extrinsic evidence could amount to "making factual evidentiary findings."[20] But in its key opinions,

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[20] *Markman v. Westview Instruments, Inc.*, 52 F. 3d 967, 981 (Fed. Cir. 1995) (en banc). The court insisted that even in "rejecting [certain] evidence as unhelpful, and resolving disputes en route to pronouncing the meaning of claim language ..., the

the Federal Circuit has never provided a valid explanation for how a battle of experts can be resolved *without* factfinding. As this Court has made clear, "[d]etermining the weight and credibility of the evidence is the special province of the trier of fact." *Inwood Labs., Inc. v. Ives Labs., Inc.*, 456 U.S. 844, 856 (1982).

Instead, the Federal Circuit has articulated three rationales for *de novo* review: *First*, that this Court either expressly or implicitly decided the issue in *Markman*; *second*, that the interpretation of any written instrument is a pure question of law; and *third*, that *de novo* review is *preferable* to deference for various reasons. None of these justifications is persuasive. The reality remains that claim construction often turns on "basic factual inquiries," *Graham*, 383 U.S. at 17.

A. Recognizing That Claim Construction May Entail Factfinding Is Entirely Consistent With This Court's Decision In *Markman*

The Federal Circuit's decision in *Cybor* offered essentially no reasoning for adopting *de novo* review of claim-construction factfinding. Instead, the Federal Circuit stated that this Court had authoritatively answered the question in *Markman*. 138 F.3d at 1455-56 & n.4. Respondents have not defended that reasoning and did not mention *Markman* in their argument at the certiorari stage. *See* Br. in Opp. v, 5, 14-30. And with good reason. *Markman* resolved

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court is *not* crediting certain evidence over other evidence or making factual evidentiary findings." *Id.*

only who shall perform the claim construction: the district court, not the jury. But that cannot defeat Rule 52(a)(6): *every* case that falls under Rule 52 by definition involves a decision by a district court, not a jury. The question presented here turns not on who shall decide, but on what is to be decided: only a pure question of law, or subsidiary factual questions as well? This Court did not answer that question in *Markman*. If anything, it articulated that the ultimate question of claim construction sometimes turns on subsidiary questions of fact—directly contrary to the Federal Circuit's belief that there are no factual issues in claim construction.

1. *Markman* came to this Court as a Seventh Amendment case. The Federal Circuit had reasoned broadly (1) that claim construction is *always* a matter of law for the court; (2) that this allocation of responsibility is consistent with the Seventh Amendment; and (3) that claim construction must *always* be reviewed *de novo*. Markman brought to this Court only the question whether the Seventh Amendment required submitting *all* claim-construction disputes to the jury. *See* Pet. at i, *Markman*, *supra* (No. 95-26).[21]

The constitutional question before this Court in *Markman* did not turn on whether claim construction involves issues of fact as well as law, or is instead a pure question of law, and this Court applied no such distinction. The Court described claim construction as a "mongrel practice" with attributes of

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[21] *See also, e.g.*, Tr. of Oral Arg., *Markman, supra*, 1996 WL 12585, at *11-12 (No. 95-26) (Markman's argument that even a claim-construction dispute based purely on the patent and the prosecution history must be submitted to the jury).

both fact and law, 517 U.S. at 378, and specifically declined to decide whether "the Seventh Amendment can be said to have crystallized a law/fact distinction ... or whether post-1791 precedent classifying an issue as one of fact would trigger the protections of the Seventh Amendment," at least presumptively. *Id.* at 384 n.10. And throughout the opinion, the Court carefully referred to the question before it as the judge/jury question, not as a law/fact question. *See, e.g., id.* at 376, 377, 380, 384, 388, 390, 391.

The *Markman* Court first stated that historical practice at the time of the Seventh Amendment's adoption did not definitively resolve the Seventh Amendment question, because common law juries had little experience with patent-infringement cases before the nineteenth century. *Id.* at 380-81; *see id.* at 375-76. Relying on precedents suggesting that judges, not juries, historically tended to construe written documents, the Court reasoned by analogy that the construction of patent claims was the kind of task historically reserved for the trial court. *Id.* at 384.

The Court then turned to "functional considerations." Noting again that claim construction presented a mixed question of fact and law, the Court asked whether, *as between juries and trial judges*, "one judicial actor is better positioned than another to decide the issue in question." *Id.* at 388. The Court concluded that "construction of written instruments is one of those things that judges often do and are likely to do better than jurors unburdened by training in exegesis." *Id.* That buttressed the Court's conclusion that claim construction should be a matter for the trial court, not the jury.

2. The standard of appellate review does not turn on the factors, such as historical practice and "functional considerations," that drove this Court's holding in *Markman*. Unlike the Seventh Amendment, Rule 52(a)(6) draws a categorical distinction between findings of fact and conclusions of law, and directs appellate courts to uphold the former unless they are "clearly erroneous." To the extent this Court's opinion in *Markman* is relevant here, it *refutes* the Federal Circuit's position, because it recognizes that claim construction can rest on factual questions (even though those factual questions need not go to a jury).

The Federal Circuit in *Cybor* stressed that in *Markman* this Court cited, in passing, a habeas corpus case applying a fact/law distinction. *See Cybor*, 138 F.3d at 1455; *Markman*, 517 U.S. at 388 (citing *Miller*, 474 U.S. at 114). But in *Markman* this Court was simply noting that it would look to "functional" considerations in allocating the judge/jury responsibility, just as the Court had done in *Miller* in parsing a fact/law distinction in the statute providing for habeas review of state-court judgments. The Federal Circuit was simply wrong in deriving from this lone citation the message that "the Supreme Court was addressing under which category, fact or law, claim construction should fall." *Cybor*, 138 F.3d at 1455. As noted, this Court disclaimed reliance on the fact/law distinction altogether. 517 U.S. at 384 n.10.

In fact, the Court in *Markman* explicitly acknowledged the "evidentiary underpinnings" of claim construction. 517 U.S. at 390. The Court acknowledged that district courts construing a patent may have to consider "an expert's proposed definition" of a patent

claim term—for example, because the term involves "a question of meaning peculiar to a trade or profession." *Id.* at 389, 390. The Court also accepted that where there is conflicting testimony, the trial judge may have to make judgments concerning the credibility of competing experts. *Id.* at 389. Indeed, "in theory there could be a case in which a simple credibility judgment would suffice to choose between experts whose testimony was equally consistent with a patent's internal logic." *Id.* For the most part, the Court noted, such credibility determinations "will be subsumed within the necessarily sophisticated analysis of the whole [patent]," a broader exercise in "exegesis" for which judges are better suited than jurors. 517 U.S. at 388, 389. But the Court said nothing to dispute that a trial judge acts as a factfinder in resolving those "evidentiary underpinnings" of claim construction. *Id.* at 390.

B. When Extrinsic Evidence Is Used To Interpret Written Instruments, Factfinding Resolves Any Disputes

When the Federal Circuit has offered an independent rationale for its no-deference rule, it has relied on the notion that patents are written instruments and must be construed purely as a matter of law.[22]

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[22] *Markman*, 52 F.3d at 978. The Federal Circuit cited a host of cases from this Court treating claim construction as a question of law. None of those cases remotely establishes that the question of law includes the consideration of extrinsic evidence. To the contrary, in those cases the question was one of law precisely *because* "it [wa]s apparent from the face of the [patent] instrument that extrinsic evidence [wa]s not needed to explain terms of art therein, or to apply the descriptions to the subject matter." *Singer Mfg. Co. v. Cramer*, 192 U.S. 265, 275 (1904);

But factfinding to construe a written instrument is entirely commonplace—in this Court's jurisprudence and elsewhere. *See* pp. 32-33, *supra*. That point has been raised in the Federal Circuit by dissenting judges, litigants, and amici, including the United States. The Federal Circuit's sole response has been repeated *ipse dixit* assertions that reliance on extrinsic evidence "does not transform that meaning from a question of law into a question of fact." *Lighting Ballast*, 744 F.3d at 1284.[23] That question-begging statement gets the analysis backwards: it is incumbent on the proponents of *de novo* review to explain why the resolution of factual disputes, potentially based on credibility judgments at a live hearing,[24] should *not* be entitled to deferential review.

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accord Mkt. St. Cable Ry. Co. v. Rowley, 155 U.S. 621, 625 (1895).

[23] *Accord Lighting Ballast*, 744 F.3d at 1285 ("[E]xperts in the science or technology may assist the court in understanding the meaning and usage of a claim term, but this does not morph the question into one of fact. ... The presentation of expert testimony on the meaning of a claim term does not transform the question from one of law to one of fact."); *id.* at 1289 ("[T]he meaning a person of ordinary skill in the art would give a term at the time of the filing of the patent application .... is not a question of fact ...."); *see also id.* at 1293 (Lourie, J., concurring) ("It is true that there may be questions concerning what a particular claim term meant to one skilled in the art at a particular time, but, in my view, when the trial judge is subjected to dueling experts selected for their views, choosing which of them to credit hardly amounts to historical fact-finding.").

[24] *See, e.g., Honeywell Int'l, Inc. v. Hamilton Sunstrand Corp.*, 523 F.3d 1304, 1314 (Fed. Cir. 2008) ("While both parties presented expert witnesses, the district court determined, after observing the witnesses' demeanor and credibility, that the resolution was not close.").

The ultimate use to which the facts will be put—here, informing the interpretation of a patent claim—does not make the inquiry any less factual in nature. *See Pullman-Standard*, 456 U.S. at 287 ("subsidiary" facts are just as entitled to deference as "ultimate" facts). Extrinsic evidence used to interpret a written instrument still raises a question of historical fact: *e.g.*, what was the accepted meaning in the relevant scientific community at the relevant time? *See* pp. 31-32, *supra*; *cf. Citibank*, 495 U.S. at 671-72 (treating industry "custom or practice" as a factual question reviewed deferentially under Rule 52(a)(6)). As Judge O'Malley of the Federal Circuit, then a district judge, has explained: "Many times [district] judges are asked to construe a term and to define what one of ordinary skill in the art at the time would have understood. The problem is that 'at the time' may have been fifteen years ago. Figuring out what was really understood or known at the time, and figuring out how to define one of [ordinary skill] in a given art are factual inquiries."[25]

Judge Lourie, concurring in *Lighting Ballast*, attempted to shift the battle to different ground; he asserted that the Federal Circuit should not adopt clear-error review of factfinding because, in his view, there should be less factfinding. 744 F.3d at 1293 ("Courts should be reluctant to go beyond the written record"). But it is too late for that. In many cases—like this one—the district court correctly concludes that expert evidence will be helpful, indeed essential, in establishing what a skilled artisan such as a poly-

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[25] Hon. Kathleen M. O'Malley et al., *A Panel Discussion: Claim Construction from the Perspective of the District Judge*, 54 Case W. Res. L. Rev. 671, 679-80 (2004).

peptide chemist would have known two decades ago.[26] The court may even resolve competing claims by experts on that point. When a case with factual findings like these goes up on appeal, the findings are reviewed for clear error; it is no answer to say that *in future cases* there should be no findings because the plain language of the patent and the prosecution history should answer all the questions. They often do not.

C. Facts Cannot Be Turned Into Law In The Name Of "Uniformity"

The Federal Circuit has repeatedly touted "uniformity" in claim construction as a reason why it should review district court decisions *de novo*.[27] If "uniformity" were a free-standing principle of appellate review, it would allow the Federal Circuit to review *everything* de novo. But uniformity is not desirable at all costs. Claim construction has contained factual elements since long before the Federal Circuit was created, as the regional courts of appeals understood. In creating the Federal Circuit, Congress did not give the new court of appeals power to circumvent Rule 52(a)(6) by recharacterizing those factual determinations as legal ones. Facts cannot be filtered out of patent litigation entirely for the sake of uniform outcomes. For instance, the same patent can be held valid in one court and invalid in

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[26] *See, e.g.*, *Eibel Process*, 261 U.S. at 65-66; *Phillips*, 415 F.3d at 1317 (explaining the "variety of purposes" for which "extrinsic evidence in the form of expert testimony can be useful to a court").

[27] *E.g.*, *Lighting Ballast*, 744 F.3d at 1277, 1280, 1286, 1287, 1288; *id.* at 1292-93 (Lourie, J., concurring).

another, if a later challenger simply does a better job litigating the content and effect of the prior art.

Before the Federal Circuit was created, the regional circuits generally acknowledged the factual component of claim construction, and reviewed such findings deferentially as a result. For instance, whereas the Federal Circuit today asserts that "the meaning a person of ordinary skill in the art would give a term at the time of the filing of the patent application .... is not a question of fact," *Lighting Ballast*, 744 F.3d at 1289, Judge Learned Hand took precisely the opposite view. "[H]ow the art understood the term," he wrote, "was plainly a question of fact; and unless the finding was 'clearly erroneous,' we are to take this definition as controlling." *Harries v. Air King Prods. Co.*, 183 F.2d 158, 164 (2d Cir. 1950).[28]

If that approach led to variations in outcome, that did not concern Congress, which created the Federal Circuit to promote uniformity on matters of "*legal* doctrine." *Christianson v. Colt Indus. Operating Corp.*, 486 U.S. 800, 813 (1988) (emphasis added) (quoting H.R. Rep. No. 97-312, at 23 (1981)). The problem Congress intended to address was legal divergence among the regional circuits over the interpretation of patent *law*, not fact-dependent district-court rulings over the interpretation of individual *patents*.

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[28] *Accord Johnson & Johnson v. Carolina Lee Knitting Co.*, 258 F.2d 593, 596 (4th Cir. 1958); *Strzalkowski v. Beltone Electronics Corp.*, 371 F.2d 237, 239 (7th Cir. 1966); *Studiengesellschaft Kohle mbH v. Eastman Kodak Co.*, 616 F.2d 1315, 1333 (5th Cir. 1980); *Wilden Pump & Eng'g Co. v. Pressed & Welded Prods. Co.*, 655 F.2d 984, 986-87 (9th Cir. 1981); *Standard Oil Co. (Ind.) v. Montedison, S.p.A.*, 664 F.2d 356, 362 (3d Cir. 1981).

Neither the Federal Courts Improvement Act of 1982[29] (which created the Federal Circuit) nor its legislative history contains any suggestion that Congress was legislating a new patent-only exception to the rule of clear-error review. To the contrary, as then-Chief Judge Markey of the Court of Customs and Patent Appeals explained, "the problem being addressed [wa]s solely at the appellate level, where the concern is the law, and only very rarely, if ever, the facts." Statement of Hon. Howard T. Markey, *Hearings Before the Subcomm. on Improvements in Judicial Machinery of the Senate Comm. on the Judiciary*, 96th Cong. 114 (1979).

Factfinding is not always uniform—as the Federal Circuit itself fully recognizes. The same patentee can end up with different results in infringement litigation against *identical products*. Or the *same patent* may survive an indefiniteness challenge in one case, only to fail the test in another case. The legal holding of definiteness in the first case does not bind the Federal Circuit (or the district court) in the second case as a matter of *stare decisis*. *E.g.*, *Mendenhall v. Cedarapids, Inc.*, 5 F.3d 1557 (Fed. Cir. 1993). That is because indefiniteness rests on factual findings. *See, e.g.*, *Graham*, 383 U.S. at 17-18. As the Federal Circuit knows and accepts, "different judgments can be reached and must be affirmed even on essentially the same evidentiary record. That is a vagary of our justice system." *Mendenhall*, 5 F.3d at 1571. And where the evidentiary record *differs* it is unsurprising that the outcome may differ as well.

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[29] Pub. L. No. 97-164, 96 Stat. 37.

"Fact-bound resolutions cannot be made uniform through appellate review, de novo or otherwise." *Cooter & Gell v. Hartmarx Corp.*, 496 U.S. 384, 405 (1990) (citation omitted). Whether the Federal Circuit reviews the facts *de novo* or deferentially, different facts can produce different results—rightly so.

The existence of factual variation between patent cases does not prevent the Federal Circuit from providing the benefits of nationwide *legal* guidance under current law. That would not change even if this Court were to reverse the no-deference rule and direct the Federal Circuit to follow Rule 52. True legal holdings—which in the claim-construction context include those announcing and applying canons of claim construction—can and do serve a law-clarifying purpose. It is *that* function that Congress created the Federal Circuit to perform.

At the same time, preclusion principles already ensure that the same patentee does not get multiple bites at the same apple. Whether an issue is characterized as legal or factual, once it is resolved against a patentee, it will be controlling in all other litigation involving the same patent and patentee. *Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found.*, 402 U. S. 313 (1971). But a litigant generally cannot be bound by litigation in which it was not represented. *Taylor v. Sturgell*, 553 U.S. 880 (2008). So some issues must be litigated anew despite the possibility of "disuniform" results.

This Court noted in *Markman* that decisions by district courts rather than juries would foster uniformity over and above what preclusion can provide, because a district court's claim construction is fully reasoned and publicly accessible and thus can have

stare decisis effect "even within a given jurisdiction." 517 U.S. at 391. In other words, district judges may choose to follow each other's claim constructions "on those questions not yet subject to inter jurisdictional uniformity under the authority of the single appeals court," *i.e.*, the Federal Circuit. *Id.* This Court's desire to promote "intrajurisdictional" stare decisis *among district courts*, *id.*, plainly has nothing to do with the standard of *appellate* review. Rather, it has everything to do with the ability of district courts, rather than juries, to set out a written, reasoned claim construction that others may read and follow. Nothing at issue here affects the settled division of labor between judge and jury that this Court prescribed in *Markman*.

D. Factfinding On Appeal Produces Poorer Decisions And Is Costly To The Patent System

Even if this were a case in which this Court were to select a standard of review, rather than simply to enforce the selection already made by Rule 52(a)(6), *de novo* review of factfinding would still be the wrong choice. The primary justification the Federal Circuit has trumpeted for the no-deference rule is the desire to maximize the potential uniformity the Federal Circuit can bring to patent law. But that argument assumes that uniformity is a virtue rather than a vice. Centralizing all decisionmaking before a single actor makes sense only if that actor will *make better decisions*. And here the Federal Circuit's role in reviewing disputed facts does not improve the system. "To replace the trier of fact with the Federal Circuit is as unfriendly to the search for truth, as it is unworkable," Judge Newman warned in *Markman*, and

her warning was prescient. 52 F.3d at 1025 n.12 (dissenting opinion).

1. Effect on District-Court Adjudication: The no-deference rule sends a clear message to district judges and litigants: claim construction in the district court is not the main event. *Cf.* Fed. R. Civ. P 52 advisory committee's note (1985). *De novo* review of claim construction continues to produce "alarming levels of appellate reversals." *Lighting Ballast*, 744 F.3d at 1311 & n.6 (O'Malley, J., dissenting) (quoting amicus brief by Professor Menell, based on data through 2011). And as one experienced district judge has explained, "to some extent, the high reversal rate demoralizes many federal district court judges." O'Malley 682 (remarks of Judge Patti Saris).

"Some district judges have responded to that message by deciding that it is better to provide little or no reasoning for their claim constructions." J. Jonas Anderson & Peter S. Menell, *Informal Deference: A Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 Nw. U. L. Rev. 1, 68 & n.320 (2014) (citing cases). They believe their explanations will promptly be discarded by the Federal Circuit, which examines the issues anew. Allowing factual findings to play their proper role—the same role they play in numerous other types of litigation that involve a degree of document interpretation—will promote better reasoning in trial-court decisions and better adjudication on appeal.

2. Effect on Appellate Adjudication: Appellate judges have, at best, limited ability to engage deeply with the science, in real time. Their lack of immersion affects the quality of their decisionmaking—

especially when they substitute their own views for the district court's.

The federal rules give district courts—but not appellate courts—tools with which to improve their understanding of scientific and technical matters and to "overcome the inherent difficulty" of resolving these subjects. *Joiner*, 522 U.S. at 149 (Breyer, J., concurring). "[E]xamination by the court" at a pretrial hearing is one example; others include the appointment of special masters, court-appointed experts suggested by the scientific community, or even specially appointed law clerks with specialized training. *Id.* at 149-50. Those tools are beginning to see wider use in patent cases,[30] following on a number of other science-focused cases, *see* Stephen Breyer, *Introduction, in* Fed. Judicial Ctr., *Reference Manual on Scientific Evidence* 6-7 (3d ed. 2011).

By contrast, an appellate court's capacity to grapple with scientific and technical questions is much more limited. The information available to an appellate judge is restricted to the record already developed, sometimes augmented by the untested assertions of a self-selecting group of amici, presented in lawyer-written briefs. *See* Wright 782 ("[T]he trial judge has the advantage of having made the initial sifting of the entire record and of having put it into logical sequence, while the appellate court has lawyers before it picking out bits and pieces of the record

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[30] *See, e.g.*, Judge James F. Holderman & Halley Guren, *The Patent Litigation Predicament in the United States*, 2007 U. Ill. J.L. Tech. & Pol'y 1, 16-17 (discussing special masters); *Monolithic Power Sys. v. O2 Micro Int'l, Ltd.*, 558 F.3d 1341, 1345-48 (Fed. Cir. 2009) (court-appointed expert appointed where the parties presented "starkly conflicting expert testimony").

to attack or defend a particular finding."). Direct interaction with experts is unavailable. And the opportunity to question counsel is measured in minutes rather than hours or days. *See Cybor*, 138 F.3d at 1477-78 (separate opinion of Rader, J.) (explaining why "[a]n appellate court has none of the[] advantages" that a district court possesses in absorbing scientific learning); *Markman*, 52 F.3d at 1021 n.11 (Newman, J., dissenting) ("No *amicus* explained how improved technological correctness—that is, truth—would be more likely to be achieved during the appellate process of page-limited briefs and fifteen minutes per side of argument.").

Furthermore, because each patent is a unique instrument, the Federal Circuit's actual interpretations of individual claim terms are of limited precedential value. "Uniformity" does not mean that particular words must mean the same thing in every claim in which they appear; a different context, or different art, can produce a different meaning. *Markman*, 496 U.S. at 390 ("[A claim] term can be defined only in a way that comports with the instrument as a whole."). And that heavy fact-dependency means that the "normal law-clarifying benefits" of *de novo* review are absent here. *Cooter & Gell*, 496 U.S. at 404 (quoting *Pierce*, 487 U.S. at 561).[31]

Another factor makes any putative "law-clarifying benefits" even more elusive: claims are read from

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[31] *See* David Krinsky, *The Supreme Court, Stare Decisis, and the Role of Appellate Deference in Patent Claim Construction Appeals*, 66 Md. L. Rev. 194, 224 (2006) (concluding that judicial interpretations of claim language are "apparently seldom used in practice" to construe the same claim language in later cases).

the perspective of a skilled artisan *at the time of the patent application*. Thus, changes in the art itself sap the Federal Circuit's interpretations of particular words or phrases of precedential value. The same artisan might interpret the same words in the same context quite differently after some years had passed. *De novo* review is not warranted for the sake of producing precedent that might be "of entirely historical interest," as this Court observed when selecting a standard of review for a somewhat comparable situation—an attorney's-fees statute that asked "not what the law now is, but what the Government was substantially justified in believing it to have been." *Pierce*, 487 U.S. at 561.

3. Effect on Settlement and Cost: Numerous commentators, including sitting federal judges, have observed that the availability of a *de novo* appeal after final judgment encourages litigants to keep litigating. *See, e.g., Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1363 (2010) (Clark, District Judge, concurring). Judge Clark observed that under the *de novo* review standard, "rejection of settlement is encouraged, and a decision to appeal is almost compelled, where counsel believes the client's position is valid, even if debatable." *Id.*

Furthermore, the fact that the Federal Circuit resolutely refuses to entertain claim-construction appeals before final judgment[32] means that reversals have hefty consequences. A reversal on claim construction, after summary-judgment motions and at least one trial, will likely result in a new trial. In a patent system where litigation expense is already

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[32] *See Portney v. CIBA Vision Corp.*, 401 F. App'x 526, 529 (Fed. Cir. 2010)

skyrocketing, the *prolongation* of litigation through summary judgment, trial, and appeal promises to be in no one's interest.

Never fear, a few voices have urged—the Federal Circuit is beginning to provide some "informal" deference, and the reversal rate is beginning to drop. *E.g., Lighting Ballast*, 744 F.3d at 1294 (Lourie, J., concurring). But as scholars have observed, the Federal Circuit's reversal rate in claim-construction appeals is still higher than other circuits'. *Id.* at 1311 (O'Malley, J., dissenting) (citing research). The Federal Circuit has now reaffirmed that factual elements of claim construction are due no extra deference. *Id.* And an essentially unreasoned, standardless form of deference—which apparently seems to consist of reversing the claim constructions the court disagrees with and affirming the ones it does agree with—will do nothing to enhance the predictability of patent appeals, or to restore the Federal Circuit to the limited role that an appellate court should play on matters of historical scientific fact.

IV. The Federal Circuit's Failure To Review The District Court's Factfinding Deferentially Led It To Misunderstand The Science And Misread The Patent

This was a case in which the *de novo* standard caused the Federal Circuit to ignore the district court's factfinding—and to run astray as a result. Shaped by nearly two decades' experience reviewing facts *de novo*, the Federal Circuit substituted its own lay understanding of Figure 1, of SEC technology, and of the prosecution history, in place of the understanding that the district court found was

scientifically correct. Any one of these errors would be enough to justify setting aside the Federal Circuit's claim construction and remanding. But as set out below, *all three* of the indicia on which the Federal Circuit relied were starkly at odds with the district court's factual findings. And respondents have never attempted to argue that any one of those findings was clearly erroneous.[33] *See Microsoft*, 131 S. Ct. at 2242. Because the facts found by the district court demonstrate that Teva's patent is not indefinite, the judgment of the court of appeals should be reversed.

A. The Federal Circuit held that Figure 1 of the patent refutes the district court's reading of the term "average molecular weight" to mean peak average. In that figure, the curves corresponding to the batches identified as having a molecular weight of 7.7 kDa have a (shared) peak that is near, but not at, 7.7 kDa. Therefore, the panel reasoned, "the M_p of the corresponding batch" is not 7.7 kDa.

But the district court had specifically resolved a factual dispute on that very point. The court found that reading Figure 1 as the Federal Circuit later did would misunderstand the scientific and statistical techniques used to create Figure 1. Peak average molecular weight is the value at the peak of a chromatogram, and Figure 1 is not a chromatogram. *See* Pet. App. 44a-45a, 49a, 126a-127a. The chromatogram "would have to be converted into the graph shown in Figure 1." *Id.* at 44a. The peak averages would fall "approximately at the peaks of the curves" in Figure 1, but not exactly, because the

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[33] *See* Br. in Opp. 19-25 (contending only that the factual findings were due no deference).

process of subdividing and converting the chromatographic data and plotting the data points would cause a shift. *Id.* at 45a, 49a (emphasis added); *see id.* at 111a-18a. Thus, "the fact that the peaks in Figure 1 do not match the listed AMWs precisely would not dissuade a person of ordinary skill in the art from concluding that AMW refers to M_p." *Id.* at 49a.

Mylan's expert contended that the peak would *not* be expected to shift, so the molecular weight at the peak of the curve in Figure 1 *was* the peak average. J.A. 374a-76a. Teva's expert explained why Mylan's expert was wrong. J.A. 1119a-20a. The district court found Teva's expert more persuasive. But instead of giving that finding the deference that Rule 52 mandates, the Federal Circuit simply eyeballed its way to its own decision accepting the view of Mylan's expert instead of Teva's.

Respondents have attempted to defend this reasoning by arguing that the district court's findings are due no deference because they "contradicted" Figure 1. Br. in Opp. 22-23. But that is question-begging: Figure 1 is not self-explanatory, and resolving what Figure 1 shows and does not show to a person of ordinary skill in the art requires the court to answer factual questions—how a graph like Figure 1 is produced by transforming a chromatogram, and what the effect of the transformation would be. The district court expressly found that Teva's answer was correct; the

Federal Circuit implicitly, and improperly, credited Mylan's.[34]

B. The panel also ascribed no significance to the district court's finding that peak average would be the "presumed meaning" of average molecular weight to a skilled artisan, because of the use of SEC. Pet. App. 43a. Peak average is the only measure that is defined by the SEC technology—it is the molecular weight corresponding to the peak of an SEC chromatogram, nothing more and nothing less. It is therefore the only measure that can be read directly from an SEC chromatogram, without any further calculation. *Id.* at 43a, 111a, 125a. Number average and weight average cannot—although there are other technologies that *would* produce those measurements directly, such as osmometry (number average) and light-scattering (weight average). J.A. 123a-24a, 521a-22a.

As the district court thoroughly understood (based in part on the opinions of Mylan's expert), calculating number average and weight average from SEC results would involve additional work, including determining either the number fraction or weight fraction of the molecular weight distribution and then performing additional calculations. J.A. 372a-

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[34] The Federal Circuit accepted respondents' argument that the average molecular weight in Figure 1, 7.7 kDa, was "closer to the M_w" than to the peak of the curve in Figure 1, which the court wrongly called "the M_p." Pet. App. 10a. As stated in text, that does not show whether the *real* M_p of that sample was 7.7 kDa. And what the Federal Circuit confidently called "the M_w" was in fact Dr. Grant's recollection, at deposition, that he had approximated the weight average as "probably around" 8.3 to 8.5 kDa. J.A. 310a. Mylan's Dr. Ryu had calculated the same figure as 12.9 kDa, J.A. 381a—considerably *farther* from 7.7.

73a, 376a-83a. And "[i]t is uncommon ... for only one of M_n or M_w to be listed when referencing data generated by SEC." Pet. App. 129a. Accordingly, the district court found that a skilled artisan would presume that average molecular weight determined by SEC means peak average. *Id.* at 43a. The Federal Circuit, on the other hand, dismissed the differences among the three measurements and concluded in effect that the use of SEC would *not* point a skilled artisan toward peak average. That is not a legal conclusion, but an impermissible second-guessing of the district court's factfinding.

C. Finally, the panel placed great weight on what it considered to be contradictory statements in the prosecution histories of two of the patents-in-suit. Both of those statements were made only after the '808 patent issued. They therefore could not possibly suffice to show that the '808 patent was indefinite *when issued.*

To the extent that this after-the-fact prosecution history bears on the construction of the '808 patent at all, obvious scientific errors carry no weight, particularly when they are later corrected. *See, e.g.*, *Rambus Inc. v. Infineon Tech. AG*, 318 F.3d 1081, 1089 (Fed. Cir. 2003) (an "incorrect statement in the prosecution history does not govern the meaning of the claims"); *Biotec Biologische Naturverpackungen GmbH v. Biocorp Inc.*, 249 F.3d 1341, 1348 (Fed. Cir. 2001); *see also* p. 29, *supra*. The Federal Circuit found the definiteness of the term fatally undermined by the statement in the prosecution of the '847 patent that the specification's expression of average molecular weight in kilodalton units "implies a weight average molecular weight." But

that statement was, *as all parties' experts agreed*, manifestly wrong. Pet. App. 52a. Peak, number, and weight average molecular weight are *all* expressed in kilodaltons. A skilled artisan would understand that the statement was akin to answering the question "Is that temperature Fahrenheit or Celsius?" with "Celsius, because it is expressed in degrees." It is a non sequitur. And subsequently, during prosecution of the '539 patent, Teva confirmed that "average molecular weight" meant "peak average molecular weight," just as the District Court found that the specification of all these patents taught.

Whether a statement contains an error—a *scientific* error, apparent to a skilled artisan—is plainly a question of fact, concerning the historical understanding of persons of skill in the pertinent art. The district court here found that the reference to "weight average" reflected obviously false non-scientific reasoning that would be apparent to any skilled artisan. Such a statement in prosecution history cannot be used to undermine the teachings of the specification. The district court's finding was entitled to deference on appeal. Instead the Federal Circuit never even acknowledged it.

* * * *

What happened here has happened in far too many cases over the last two decades: the district court undertook a conscientious effort to grapple with the technology, understand the usage in the art, and construe the patent accordingly. That effort entailed months of expert discovery, two *Markman* hearings, and a lengthy written opinion. The district court made a reasoned finding that a person skilled in the art would understand Teva's patent. Yet the Federal

Circuit panel—misunderstanding the patent specification and disregarding factual findings that should have been controlling—substituted its own lay understanding of the patent and held it indefinite. To reverse this flawed outcome and prevent more like it, this Court should direct the Federal Circuit to apply Rule 52(a)(6) to patent cases just as the other courts of appeals apply it to every other type of case.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

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APPENDIX

STATUTORY APPENDIX

1. 35 U.S.C. § 103(a) (2006) provided:

Conditions for patentability; non-obvious subject matter

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. 35 U.S.C. § 112 (2006) provided:

Specification

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A claim may be written in independent or, if the nature of the case admits, in dependent or multiple dependent form.

Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

A claim in multiple dependent form shall contain a reference, in the alternative only, to more than one claim previously set forth and then specify a further limitation of the subject matter claimed. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim. A multiple dependent claim shall be construed to incorporate by reference all the limitations of the particular claim in relation to which it is being considered.

An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

3. Federal Rule of Civil Procedure 52 provides:

Findings and Conclusions by the Court; Judgment on Partial Findings

(a) Findings and Conclusions.

(1) *In General.* In an action tried on the facts without a jury or with an advisory jury, the court must find the facts specially and state its conclusions of law separately. The findings and conclusions may be stated on the record after the close of the evidence or may appear in an opinion or a memorandum of decision filed by the court. Judgment must be entered under Rule 58.

(2) *For an Interlocutory Injunction.* In granting or refusing an interlocutory injunction, the court must similarly state the findings and conclusions that support its action.

(3) *For a Motion.* The court is not required to state findings or conclusions when ruling on a motion under Rule 12 or 56 or, unless these rules provide otherwise, on any other motion.

(4) *Effect of a Master's Findings.* A master's findings, to the extent adopted by the court, must be considered the court's findings.

(5) *Questioning the Evidentiary Support.* A party may later question the sufficiency of the evidence supporting the findings, whether or not the party requested findings, objected to them, moved to amend them, or moved for partial findings.

(6) *Setting Aside the Findings.* Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility.

(b) Amended or Additional Findings. On a party's motion filed no later than 28 days after the entry of judgment, the court may amend its findings—or make additional findings—and may amend the judgment accordingly. The motion may accompany a motion for a new trial under Rule 59.

(c) Judgment on Partial Findings. If a party has been fully heard on an issue during a nonjury trial and the court finds against the party on that issue, the court may enter judgment against the party on a claim or defense that, under the controlling law, can be maintained or defeated only with a favorable finding on that issue. The court may, however, decline to render any judgment until the close of the evidence. A judgment on partial findings must be supported by findings of fact and conclusions of law as required by Rule 52(a).

RESPONDENT'S BRIEF

No. 13-854

In The Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA NEUROSCIENCE, INC., AND YEDA RESEARCH AND DEVELOPMENT CO., LTD., PETITIONERS,

v.

SANDOZ INC., MOMENTA PHARMACEUTICALS, INC., MYLAN PHARMACEUTICALS INC., MYLAN INC., AND NATCO PHARMA LTD., RESPONDENTS.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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QUESTIONS PRESENTED

Whether the court of appeals properly concluded that claim construction involves a pure question of law, and thus the standard of appellate review of the lower court's interpretation of a patent's claims is de novo.

If claim construction could entail factual findings that are reviewed for clear error, whether the court of appeals correctly concluded that the language of the claims, specification, and prosecution history rendered the patent claims at issue "insolubly ambiguous" and thus, *a fortiori*, indefinite under this Court's recent decision in *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120 (2014).

CORPORATE DISCLOSURE STATEMENTS

Sandoz Inc. is an indirect wholly-owned subsidiary of Novartis AG. No other publicly held company owns 10% or more of the stock of Sandoz Inc.

Momenta Pharmaceuticals, Inc. is a publicly held corporation. No parent corporation or other publicly held corporation owns more than 10% of Momenta's stock.

Mylan Inc. is a publicly held corporation. No parent corporation or publicly held corporation owns more than 10% of its stock. Mylan Pharmaceuticals Inc. is wholly owned by Mylan Inc.

Natco Pharma Ltd. is a publicly held corporation. No parent corporation or publicly held corporation owns more than 10% of its stock.

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INTRODUCTION

The Federal Circuit reviewed the public record that Teva created to define the metes and bounds of its invention and reached the legal conclusion that the patent claims at issue here are indefinite. That judgment is correct and should be affirmed under any standard of review.

Teva complains that the Federal Circuit has adopted an exception to Rule 52's clearly erroneous standard. But Rule 52 does not resolve this case; the Court's decision in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), does. Rule 52 applies only to findings of fact, not to conclusions of law. And in *Markman*, which Teva tries to marginalize, this Court concluded that all interpretive issues in claim construction are "purely legal," including those involving consideration of evidence outside the four corners of the patent and its prosecution history. *Id.* at 391. De novo appellate review follows from that holding. A patent's claims, specification, and prosecution history form the public record of the monopoly bestowed on the patentee by the United States. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120 (2014). The meaning of that legal grant should be reviewed de novo, as are the meaning of statutes and other legal instruments that define for the public what is lawful and unlawful. Any "fact" inquiries relevant to such rulings are properly considered "legislative facts" and reviewed de novo.

Even if this Court were to conclude that some questions underlying claim-construction rulings could be adjudicative facts within the meaning of Rule 52, that would not change the outcome here. Any line between fact and law would have to be carefully drawn so that the meaning of patents is readily ascertainable. What is considered factual must be limited to scientific principles or other issues whose truth is determined separate and apart from the particular patent asserted. "Facts" that may be reviewed deferentially must not include any interpretation of the patent at issue and its prosecution history—that is a legal question. A contrary ruling would eviscerate *Markman*, which, at the very least, established that the meaning of the public record is a legal question. Moreover, giving deference to purported "findings" based on a litigation expert's present reading of a patent and its prosecution history would severely undermine the certainty and notice of patent boundaries that are critical to an efficient patent system. Indeed, such deference would encourage parties to engage in a battle of experts and lead district courts to over-rely on paid litigation experts.

Accordingly, if this Court decides that there are factual issues governed by Rule 52, it should define a workable boundary between factual findings and legal claim construction, and apply that line to this case to provide guidance to lower courts. The Federal Circuit's indefiniteness determination is correct under any standard of review because the court did not disturb anything that could be considered a factual

finding. What the district court did here was merely "credit" a paid litigation expert's interpretation of the patents and prosecution history. Although a district court may consider such an opinion in drawing its own legal conclusions, that does not convert those legal conclusions into "findings" subject to clear-error review. A patentee should not be permitted to use a litigation expert to amend the hopelessly ambiguous public record it created.

The judgment should be affirmed.

STATEMENT

A. Statutory Framework

Through a patent, the government confers a monopoly by allowing a patent holder "to exclude others from making, using, offering for sale, or selling the invention." 35 U.S.C. § 154(a)(1).[1] For this right to exclude, the patentee must fully disclose the invention and dedicate it to the public after the patent expires. *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 480-81 (1974).

The Patent Act requires that a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as [the] invention." 35 U.S.C. § 112, ¶ 2. The specification must "contain a written description of the invention, and of the manner and

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[1] References to Title 35 are to the 2006 edition. Teva Br. 5 n.4.

process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains * * * to make and use the same." *Id.*, ¶ 1. The patent's claims, specification, and drawings, as well as its prosecution history, set forth the scope of the monopoly and what remains available to the public. *Markman*, 517 U.S. at 373-74; *Nautilus*, 134 S. Ct. at 2128.

Section 112, ¶ 2 requires that the public record of this legal instrument must "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus*, 134 S. Ct. at 2129. Where, as here, the patents claim a "variant" of the prior art, the law requires "precise descriptions of the new characteristic for which protection is sought." *General Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938). "[A]bsent a meaningful definiteness check * * * patent applicants face powerful incentives to inject ambiguity into their claims." *Nautilus*, 134 S. Ct. at 2129. Such ambiguity "diminish[es] the definiteness requirement's public-notice function and foster[s] the innovation-discouraging 'zone of uncertainty,' against which this Court has warned." *Id.* at 2130 (quoting *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942)). "'[T]he patent drafter is in the best position to resolve the ambiguity in * * * patent claims,'" and its failure to do so renders the patent invalid. *Id.* at 2129; *see* 35 U.S.C. § 282, ¶ 2(3).

"Claim construction" is the interpretation by a court of what a patent claim means. *See Markman*,

517 U.S. at 373-74. It is a pivotal part of every patent infringement suit. Where a claim lacks sufficient definiteness to be construed, a court does not read in a meaning; it holds the claim invalid. *See Nautilus*, 134 S. Ct. at 2129-30.

Because claim construction involves delineating the legal scope of the patent grant, the Federal Circuit for nearly two decades has reviewed all aspects of claim construction de novo. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1451 (Fed. Cir. 1998) (en banc); *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1276-77 (Fed. Cir. 2014) (en banc).

B. The Public Record Of Teva's Patents

Teva markets Copaxone®, a widely prescribed treatment for multiple sclerosis. Without generic competition, Copaxone® treatments have cost individual patients tens of thousands of dollars per year. CAFC J.A. 19635.

Copaxone® is a form of copolymer-1. The patents at issue cover copolymer-1 and methods of manufacturing it. Pet. App. 4a. These patents share a common specification and trace back to the same patent application—that is, they are part of the same patent "family." Pet. App. 4a, 27a & n.2.

Copolymer-1 is not new; its use to treat multiple sclerosis was discovered by 1971. J.A. 1143a; CAFC J.A. 26052-53, 49258. Earlier patent protection

expired in 1991. Teva obtained the new patents here by contending that it had "improved" copolymer-1 by selecting portions with a particular "molecular weight" or "average molecular weight" that were less toxic but still effective. CAFC J.A. 18180, 18199. Claim 1 of U.S. Patent No. 5,800,808 ('808 patent) is representative, claiming a method of manufacturing "copolymer-1 having a molecular weight of about 5 to 9 kilodaltons" (kDa). Pet. App. 150a.

It is undisputed that the term "molecular weight" in these claims is ambiguous on its face. Pet. App. 8a, 42a. As Teva conceded, there are several ways to describe the molecular weight of copolymer-1, including weight average molecular weight (M_w), number average molecular weight (M_n), and peak molecular weight (M_p). Pet. App. 4a. The precise measure of molecular weight is critical to defining the claimed drug: the same sample of copolymer-1 will have a different molecular weight value depending on whether M_w, M_n, or M_p is reported. Pet. App. 4a-5a. Without knowing the measure, the scope of the claims is indiscernible.

This is not a situation involving "the inherent limitations of language." *Nautilus*, 134 S. Ct. at 2128. It would have been simple for Teva to specify the measure embodied in its claims. Yet Teva chose not to state whether it was weight, number, or peak even though, according to Teva, the effectiveness and reduced toxicity of the claimed substance depend on its precise molecular weight.

During prosecution of this family of patents, the Patent and Trademark Office (PTO) reviewed the common specification and the proposed claims and recognized that Teva's failure to specify the measure rendered the claims indefinite. On two separate occasions, a PTO Examiner rejected Teva's claims for this very reason: "The term 'average' molecular weight * * * is meaningless as a limitation without specifying its basis, e.g. weight average molecular weight, number average molecular weight, etc." J.A. 1299a; *accord* J.A. 1343a ("the term 'average molecular weight' * * * is indefinite since its method of measurement is not specified").

Teva overcame these separate rejections by giving irreconcilable answers—once defining the term to mean "weight" average molecular weight and once defining it to mean "peak." Pet. App. 9a, 51a; J.A. 1322a, 1355a. In response to Teva's "weight" answer, the PTO granted Teva one patent, U.S. Patent No. 6,620,847 ('847 patent). J.A. 1326a, 1195a. In response to Teva's "peak" answer, the PTO granted Teva another patent, U.S. Patent No. 6,939,539 ('539 patent). J.A. 1358a, 1241a. In each instance, the PTO withdrew the indefiniteness rejection solely because Teva identified a particular measure of weight. Pet. App. 9a.

This public record compounded the claims' inherent ambiguity. Momenta spent "years of scientific research" to determine the molecular weight of the copolymer-1 that Teva's patents supposedly disclosed. J.A. 162a; *see* CAFC J.A. 20543-46; J.A. 1131a

(Natco's efforts to determine molecular weight in patents). And when Sandoz and Momenta (together, Sandoz) submitted their abbreviated new drug application (ANDA) seeking FDA approval to market a generic version of Copaxone®, Teva contended (incorrectly) that the only way they could have replicated the copolymer-1 in Copaxone® is to have stolen trade secrets. CAFC J.A. 491-94.

C. Proceedings Below

1. The District Court Relied on a Litigation Expert's "Interpretation" of the Public Record to Read "Peak" Into Teva's Ambiguous Claims.

In response to Sandoz's ANDA, Teva filed suit, alleging patent infringement and theft of trade secrets. CAFC J.A. 479. That suit was consolidated with Teva's subsequent patent infringement suit against Mylan and Natco (together, Mylan), which had filed their own ANDA. J.A. 63a, 69a.

a. In district court, Sandoz and Mylan contended that Teva's "molecular weight" claims were invalid for indefiniteness.

The district court recognized that "average molecular weight" "has no 'ordinary and customary meaning'" and that the claims "are silent as to the meaning." Pet. App. 42a. It nevertheless held them not indefinite by reading "peak" into the claims. Pet. App. 62a. In so holding, the district court applied the "amenable to construction" and "insolubly ambiguous" standards for indefiniteness, Pet. App. 30a,

that this Court has since rejected as too stringent, *Nautilus*, 134 S. Ct. at 2129-30.

The district court relied on declarations of Teva's expert, Gregory Grant, prepared solely for this litigation. Portions of Grant's declarations described relevant background scientific principles, in a section entitled "BACKGROUND POLYPEPTIDE AND MOLECULAR WEIGHT PRIMER." Pet. App. 94a-118a (Grant *Mylan* Decl.); *accord* J.A. 111a-29a (Grant *Sandoz* Decl.). For example, he explained how a particular method of measurement called size exclusion chromatography (SEC) works. *E.g.*, Pet. App. 107a-11a. And he explained (as all agreed) that the SEC method produces peak, weight, and number average molecular weight. Pet. App. 106a-07a ¶39; *see* Pet. App. 43a.

The district court also purported to "credit" a section of the expert's declarations entitled "CLAIM CONSTRUCTION." Pet. App. 118a. The declaration states, "[i]n the paragraphs that follow, I set forth my opinion as to the proper interpretation of phrases or terms in the claims of the patents-in-suit." Pet. App. 118a ¶54; *see* J.A. 129a ¶44 (same). It was these "Claim Construction" paragraphs from which the district court drew its conclusion that the patents mean "peak." *See, e.g.*, Pet. App. 43a-44a, 48a-49a, 52a.

For example, the district court relied on Grant's assumptions and conclusions based on what the specification did and did not include regarding the SEC method. Pet. App. 43a (citing J.A. 138a ¶61), 48a (citing Pet. App. 125a ¶70). The court also relied on Grant's effort to explain away Figure 1 in the patent. It was undisputed that the peaks of the Figure's three curves (as measured by the molecular weight values on the horizontal axis) do not match the average molecular weight values in the legend in the Figure's top right corner:

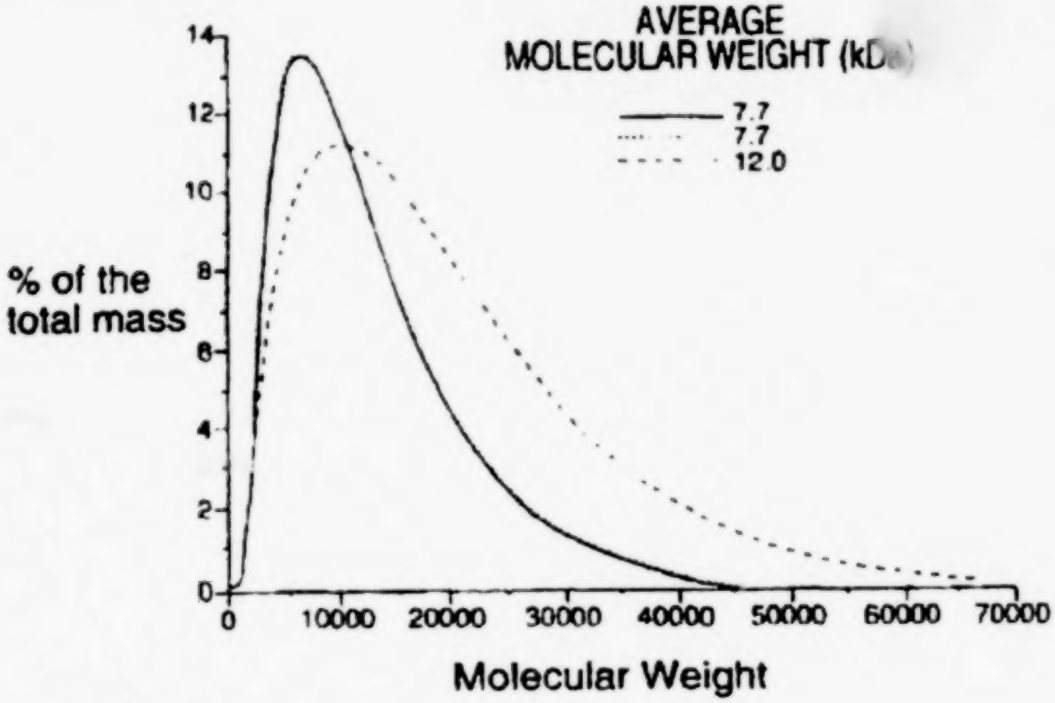

FIG. 1

J.A. 1141a. Based on Grant's assumption of an unspecified margin of error due to a slight shift caused by creation of the graph, the district court concluded that the Figure "would not dissuade a person of ordinary skill in the art from concluding that [average

molecular weight] refers to Mp in the context of the patents-in-suit." Pet. App. 49a (citing Pet. App. 111a-18a ¶¶44-53; J.A. 138a-39a ¶62, 348a-49a ¶7).

The district court similarly relied on Grant's reading of the prosecution history to disregard one of Teva's conflicting public statements to the PTO. Citing one of Grant's "Claim Construction" paragraphs, the district court concluded that because Teva's explanation for one of its answers—that "kilodalton units implies a weight average molecular weight"—was scientifically incorrect, "a person of ordinary skill in the art would not rely on it." Pet. App. 52a (citing J.A. 140a ¶64). The district court so concluded, even though Teva's answer to the PTO regarding the type of weight—"weight average molecular weight"—resulted in issuance of a patent.

b. After a bench trial on other issues, the court enjoined respondents from entering the market until expiration of the latest expiring patent, the '808 patent, on September 1, 2015. Pet. App. 78a-81a.

2. *The Court of Appeals Held that the Public Record Rendered Teva's Patents Indefinite.*

In a unanimous decision, the Federal Circuit held that Teva's "molecular weight" claims were indefinite even under its very strict, now-rejected "insolubly ambiguous" test. Pet. App. 6a-10a. Accepting the background scientific facts, the court engaged in "*de novo* review of the district court's indefiniteness holding"

and reached a different legal conclusion. Pet. App. 10a.

The Federal Circuit recognized that the claims "contain an ambiguity because their plain language does not indicate which average molecular weight measure is intended." Pet. App. 8a. Looking at the prosecution history, the court concluded that Teva's two "prosecution statements directly contradict each other and render the ambiguity insoluble." Pet. App. 8a-9a.

As to Teva's "peak" answer, the court explained that "[t]he only basis upon which the Examiner could have agreed that the '539 patent claims were not indefinite was that 'molecular weight' means M_p." Pet. App. 9a. As to Teva's "weight" answer, the court of appeals acknowledged that Teva's explanation "contains an evident scientific error." *Ibid.* But it emphasized that the answer nonetheless led to issuance of a patent: "the only basis for the Examiner's withdrawal of the indefiniteness rejection of the '847 patent claims was that the same term means M_w." *Ibid.* The Federal Circuit concluded that "Teva's two definitions cannot be reconciled." *Ibid.*

The Federal Circuit further held that "[t]he specification does not resolve the ambiguity." *Ibid.* While acknowledging Teva's expert's interpretation of the specification and prosecution history, the court concluded that "Dr. Grant's testimony does not save [these] claims from indefiniteness." Pet. App. 9a-10a. The court observed that all the experts, including

Grant, agreed that M_p and M_w also can be obtained from the SEC method. Pet. App. 10a. As for Figure 1, the Federal Circuit noted that Grant's own calculation of *weight* average molecular weight (8.3 to 8.5 kDa) for the two overlapping curves in Figure 1 was closer to the legend's 7.7 kDa than his measurement of the *peak* in those curves. *Ibid.* (citing J.A. 310a); *see* Pet. App. 127a. Given that neither Grant's calculation for M_w nor his calculation for M_p matched the 7.7 kDa in the Figure's legend, but both were close, the court reasoned that it is "difficult to conclude that M_p is the intended measure." Pet. App. 10a.

SUMMARY OF ARGUMENT

The Court should affirm the judgment of indefiniteness for either of two independent reasons.

I. The Federal Circuit correctly reviews all aspects of claim construction de novo. Plenary review follows directly from this Court's decision in *Markman*, which held that all interpretive issues in claim construction—including any issues arising from the consideration of evidence outside the patent—are treated as "purely legal." 517 U.S. at 391. Rule 52 and its clear-error standard do not apply to issues of law.

Markman's determination that seemingly "factual" issues in claim construction are treated as purely legal is consistent with this Court's use of interpretive aids to construe statutes and other legal instruments defining public rights and duties. The scope of a patent claim is governed by the public

record: the claim language, specification, and prosecution history. Background scientific evidence outside that public record is simply a tool to discern the legal metes and bounds of the government's grant and the remaining public domain. This Court has long used such tools to determine "legislative" facts without deference to lower courts.

Plenary review of all aspects of claim construction is confirmed by this Court's approach to deciding whether particular issues are reviewed de novo, as well as the Court's historical practice of independently reviewing claim-construction determinations. Teva's analogies to other areas of law are inapt. Unlike these other areas, claim construction establishes a legal ruling that defines what is and is not available to the public.

Finally, the need for uniformity remains as critical today as it was when this Court decided *Markman*. The *Markman* Court emphasized that uniformly interpreting the scope of each patent is critical to the patent system and that the Federal Circuit is key to achieving that uniformity. This Court thus treated a ruling on the meaning of a patent claim as a question of law that, once finally decided, is *stare decisis* as the one and only meaning of that patent claim.

This Court should reaffirm here that all aspects of claim construction are purely legal, and thus are reviewed de novo.

II. If the Court concludes that claim construction may include factual findings that warrant

appellate deference, it must carefully draw the line between fact and law. "Facts" must be strictly limited to scientific principles and other issues that are separate and apart from the asserted patent. The significance of the claim language or the patent's written description and prosecution history are not factual issues for experts to debate. They turn on the public record and are for courts to decide as matters of law.

This line follows from this Court's cases. Any contrary line would severely undermine the public notice function at the core of the patent system. The scope of the monopoly granted by the United States and binding against the public must not depend on an expert's post hoc, litigation-driven interpretation.

Teva avoids clearly elucidating where it would draw the line between fact and law. But it suggests that a district court's crediting of a litigation expert's interpretation of the patent and its prosecution history (including the expert's inferences and assumptions from that public record) can be a "fact." That cannot be squared with *Markman*, which at the very least held that all interpretive issues are "purely legal." 517 U.S. at 391.

If this Court concludes that claim construction includes both legal and factual components, it should both define and apply its standard for distinguishing the two to provide guidance to lower courts. The Federal Circuit held Teva's facially ambiguous claims indefinite, and that holding is correct under any

standard. The holding fully accords with the three "facts" raised by Teva: *First*, the Federal Circuit expressly acknowledged Teva's contention that its statement to the PTO that a kilodalton implies M_w "contains an evident scientific error." Pet. App. 8a. But a mistaken rationale does not eliminate the definition actually given. The court thus correctly focused on Teva's irreconcilable "weight" and "peak" answers to the PTO, each of which resulted in issuance of a patent with the same specification and the same claim term. Teva's irreconcilable answers simply compound the ambiguity on the face of the claims.

Second, turning to the specification, the court of appeals expressly recognized that M_p can be "read directly from a plot of SEC data," whereas "some calculations" are required to obtain M_n and M_w. Pet. App. 10a. But the court also correctly concluded that the reference to SEC was not enough to cure the claims' facial ambiguity: it was undisputed that a skilled artisan could use SEC data to obtain all three potential measurements.

Third, the indefiniteness holding is fully consistent with the only plausible factual determination regarding Figure 1: that a slight shift in the curves of the graph would be expected in the creation of such a graph. Teva's own expert's calculation of the M_w of the curves was within the margin of error he expected from such a shift, so both M_w and M_p were consistent with the numbers in the Figure's legend. As the Federal Circuit correctly concluded, that "makes it

difficult to conclude that M_p is the intended measure." Pet. App. 10a (citing J.A. 310a).

The judgment should be affirmed.

ARGUMENT

I. THE FEDERAL CIRCUIT CORRECTLY REVIEWS ALL ASPECTS OF CLAIM CONSTRUCTION DE NOVO.

As this Court has explained, "Rule 52(a) does not furnish particular guidance with respect to distinguishing law from fact"; that distinction must be resolved by standards outside Rule 52. *Pullman-Standard v. Swint*, 456 U.S. 273, 288 (1982). In multiple contexts, this Court has decided whether an issue should be treated as one of law to which no deference is owed, or as one of fact to be reviewed deferentially, by assessing which judicial actor is better positioned to determine the question at issue. This law/fact inquiry turns on whether a judicial actor reviewing the legal standards and the record is more likely to arrive at the correct conclusion, or whether the initial factfinder is better positioned to do so because the credibility of witnesses is pivotal to the issue at hand. *See Miller v. Fenton*, 474 U.S. 104, 114 (1985).

Applying these considerations to claim construction, this Court concluded in *Markman* that all "interpretive issues" of claim construction—even those arising from consideration of evidence outside the patent and its prosecution history—are treated as "purely legal." 517 U.S. at 391. The proper

construction of a patent turns fundamentally on its claims, specification, and prosecution history, not the credibility of witnesses. Any facts used to discern that meaning are simply "legislative facts," to which no deference is owed.

De novo review follows from the holding and rationale of *Markman*. "[D]ecisions on 'questions of law' are 'reviewable *de novo*.'" *Highmark Inc. v. Allcare Health Mgmt. Sys., Inc.*, 134 S. Ct. 1744, 1748 (2014). Rule 52 and its clear-error standard have no part to play. *Pullman-Standard*, 456 U.S. at 287.

A. De Novo Review Follows From *Markman*.

1. Markman *Forecloses Teva's Proposal to Distinguish Facts from Law in Construing Claims.*

Teva and the government acknowledge that under *Markman* claim construction is ultimately a question of law reviewed de novo. Teva Br. 27; US Br. 10. They contend, however, that "factual findings" underlying claim construction should be reviewed for clear error—although the government fundamentally disagrees with Teva about which issues are "factual," US Br. 12, 22-23, 26-31. Teva and the government give *Markman* short shrift, contending that it "resolved only who shall perform the claim construction" and "carefully referred to the question before it as the judge/jury question, not as a law/fact question." Teva Br. 37-39; US Br. 16-17.

But *Markman*'s articulation of the question presented refutes that contention: the Court asked whether claim construction "is *a matter of law* reserved entirely for the court, or subject to a Seventh Amendment guarantee that a jury will determine the meaning of any disputed term of art about which expert testimony is offered." 517 U.S. at 372 (emphasis added). The Court's ultimate conclusion answered that question: the Court "treat[s] interpretive issues"—including subsidiary factual questions, even when they involve expert credibility—"as purely legal." *Id.* at 391.

In reaching that conclusion, the *Markman* Court considered whether the Seventh Amendment requires *any* disputed portion of claim construction to be resolved by a jury. *Id.* at 372, 377-78. According to the Court, claim construction presented a unique problem because it is a "mongrel practice" that involves "construing a term of art following receipt of evidence." *Id.* at 378. Concluding that historical practices provided no guidance, the Court turned to its existing precedent, relying on Justice Curtis's characterization of claim construction as "'a question of law.'" *Id.* at 384 (quoting *Winans v. Denmead*, 56 U.S. (15 How.) 330, 338 (1854)). Rejecting the petitioner's attempts to dismiss Justice Curtis's conclusion, this Court recognized that early cases confirmed that claim construction presents a legal question and credited early treatises making this point. *Id.* at 385-88.

Indeed, the Court referenced Walker's 1895 treatise in which he concluded, in the Court's words, that "matters of claim construction, *even those aided by expert testimony*, are questions for the court," that is, "'questions of law.'" *Id.* at 387 (quoting A. Walker, Patent Laws § 189, at 173 (3d ed. 1895)) (emphasis added). The Court also cited other treatises that used "[v]irtually the same description of the court's use of evidence in its interpretive role" to conclude that a "'court proceeds upon its own responsibility, as an *arbiter of the law*.'" *Id.* at 387-88 (quoting 2 W. Robinson, Law of Patents § 732, at 481-83 (1890)) (emphasis omitted in part).

Ultimately, however, the Court resolved the case by turning to *Miller v. Fenton*. *See Markman*, 517 U.S. at 388. *Miller* was not a Seventh Amendment case; it addressed whether the voluntariness of a confession should be treated as a factual question, and thus subject to deference on federal habeas review, or instead as a question of law. 474 U.S. at 105-06. *Miller* decided the "fact/law" issue by looking at functional considerations that dictate which judicial actor is better positioned to decide the issue in question. *Id.* at 114-17. The *Miller* Court concluded that the ultimate question of voluntariness should be treated "as a legal inquiry requiring plenary federal review." *Id.* at 115. Because "assessments of credibility and demeanor are not crucial to the proper resolution" of that issue, the reviewing court was in as good a position to decide it as the factfinder. *Id.* at 116-17. *Miller* contrasted this mixed question of law and fact,

which it treated as purely legal, from subsidiary issues (such as "the length and circumstances of the interrogation"), which remained "factual." *Ibid.*

Markman built upon *Miller*, but given the different context of claim construction, held there were no subsidiary "factual" issues. *Markman*, 517 U.S. at 388-90. As with the legal issue of voluntariness, the *Markman* Court concluded that any credibility assessments are not crucial to the proper construction of a claim. *Id.* at 389. Rather, issues such as the credibility of experts would ordinarily be "subsumed within the necessarily sophisticated analysis of the whole document, required by the standard construction rule that a term can be defined only in a way that comports with the instrument as a whole." *Ibid.* That is, any subsidiary factual issues in claim construction are properly viewed through the lens of interpreting the patent. Applying the considerations in *Miller*, the Court concluded that claim construction should be committed to the judge because it is a legal question "notwithstanding its evidentiary underpinnings." *Id.* at 390.

Contrary to Teva's assertion, *Markman* did not reference *Miller* simply to explain "that it would look to 'functional' considerations in allocating the judge/jury responsibility, just as the Court had done in *Miller* in parsing a fact/law distinction." Teva Br. 40. Quoting *Miller*, the Court explained that "'the fact/law distinction at times has turned on a determination that * * * one judicial actor is better positioned than another to decide the issue in question,'" and

then concluded, "[s]o it turns out here, for judges, not juries, are the better suited to find the acquired meaning of patent terms." *Markman*, 517 U.S. at 388. For that reason, the Court held that all aspects of claim construction are legal.[2]

That this was the Court's holding is bolstered, not undermined, by *Markman*'s recognition that factual underpinnings sometimes arise. *Contra* Teva Br. 40-41; US Br. 17-18. Notwithstanding those factual underpinnings, the Court held that the whole process is "*purely legal.*" *Markman*, 517 U.S. at 390-91 (emphasis added). The Court emphasized that this holding promotes "uniformity in the treatment of a given patent" by making the authoritative construction of the patent *stare decisis*. *Ibid.*; *see Vail v. Arizona*, 207 U.S. 201, 204 (1907) ("under the doctrine of *stare decisis*, the question should no longer be considered an open one," even if preclusion principles would not apply). That is, *Markman* concluded that the construction of a patent claim, once decided, is binding legal precedent, meaning that all aspects, including any subsidiary fact-like issues, are treated as purely legal.

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[2] Teva argues that a footnote in *Markman* "disclaimed reliance on the fact/law distinction altogether." Teva Br. 40. Teva is wrong. The Court simply said that because its existing precedent resolved the question presented, it had no reason to decide whether *Seventh Amendment analysis* will always turn on a distinction between law and fact. 517 U.S. at 384 n.10.

De novo review follows directly from that holding. *Highmark*, 134 S. Ct. at 1748 ("[D]ecisions on 'questions of law' are 'reviewable *de novo*.'").

2. *Any Factual Underpinnings to Claim Construction Are "Legislative Facts."*

a. The *Markman* Court's conclusion that what may seem "factual" should be treated as "purely legal" for purposes of claim construction is consistent with this Court's approach to "legislative"—as opposed to "adjudicative"—facts. Fed. R. Evid. 201 advisory comm. notes (1972). Adjudicative facts are those involving the dispute between the "'immediate parties—who did what, where, when, how, and with what motive or intent.'" *Ibid.* These facts "'normally go to the jury in a jury case.'" *Ibid.* Legislative facts, by contrast, are those that transcend the particular dispute and are relevant "to legal reasoning and the lawmaking process, whether in the formulation of a legal principle or ruling by a judge." *Ibid.*; *see* Robert E. Keeton, *Legislative Facts and Similar Things: Deciding Disputed Premise Facts*, 73 Minn. L. Rev. 1, 11 (1988); Allison Orr Larsen, *Confronting Supreme Court Fact Finding*, 98 Va. L. Rev. 1255, 1256-57 (2012). Because legislative facts inform a court's function in deciding and formulating a legal principle, they are for the court alone.

Moreover, although legislative facts may be introduced in traditional evidentiary hearings, they need not be, and they are reviewed without deference. *See* Fed. R. Evid. 201 advisory comm. notes (1972)

(legislative facts should not be restricted by traditional or formal requirements); Keeton, *supra*, at 22. This Court often considers such facts whether or not they have been considered by a trial court or even introduced into the record. Larsen, *supra*, at 1257-59.[3]

Markman recognizes the same role for legislative facts in claim construction: such facts are not specific to the dispute between the parties but instead help establish a legal rule, namely, the "'scope of a patent grant.'" *Markman*, 517 U.S. at 373. Whatever is not specifically claimed remains available to the public. *General Electric*, 304 U.S. at 369. Anyone stepping over the line into the patentee's right to exclude faces potentially serious consequences, including liability for infringement damages, attorneys' fees, and an injunction. 35 U.S.C. §§ 283-85. Any facts the court uses in claim construction are simply tools to determine the scope of that legal grant.

Indeed, claim construction involves precisely the same type of "facts" that courts regularly use to construe statutes and constitutional provisions, namely, dictionaries and other extrinsic background sources.

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[3] *See, e.g.*, *Toyota Motor Mfg., Ky., Inc. v. Williams*, 534 U.S. 184, 199 (2002) (whether carpel tunnel syndrome is a debilitating condition under the ADA); *Detroit Edison Co. v. NLRB*, 440 U.S. 301, 318 (1979) (sensitivity of a human being to disclosure of information about competence); *Hawkins v. United States*, 358 U.S. 74, 77-78 (1958) (effect on marriage of adverse testimony from spouse).

This Court has long relied upon such sources, even when technical terms of art are involved, without suggesting that such reliance gives rise to subsidiary factual issues that must be reviewed deferentially. *See, e.g.*, *Taniguchi v. Kan Pac. Saipan, Ltd.*, 132 S. Ct. 1997, 2002-04 (2012) ("Based on *our survey* of the relevant dictionaries, we conclude that the ordinary or common meaning of 'interpreter' does not include those who translate writings." (emphasis added)); *Nix v. Hedden*, 149 U.S. 304, 307 (1893) ("[U]pon such a question dictionaries are admitted, not as evidence, but only as aids to the memory and understanding of the court."). Claim construction is closely akin to statutory interpretation: both seek to determine the understanding of terms at a particular time, and both inform the public of what they can and cannot do (what conduct is lawful, and what is not). *See Perrin v. United States*, 444 U.S. 37, 42 (1979). This Court consistently uses legislative facts—including choosing particular definitions, and even particular dictionaries—without deference to lower courts. *See, e.g.*, *MCI Telecomms. Corp. v. AT&T*, 512 U.S. 218, 225-28 (1994).

Rightly so, because, as the courts of appeals have recognized, Rule 52's clear-error standard does not apply to legislative facts. *Doe v. Prosecutor*, 705 F.3d 694, 697 n.4 (7th Cir. 2013) (clear-error standard applies to adjudicative, not legislative, facts); *United States v. Singleterry*, 29 F.3d 733, 740 (1st Cir. 1994) (courts of appeals "need not defer to the lower court's assessment" of "[l]egislative facts"); *Dunagin v. City*

of Oxford, 718 F.2d 738, 748 n.8 (5th Cir. 1983) (en banc) (plurality opinion); *Menora v. Illinois High Sch. Ass'n*, 683 F.2d 1030, 1036 (7th Cir. 1982) (on petition for rehearing) ("clearly-erroneous standard does not apply" to "a legislative fact"). Speaking for the Court in *Lockhart v. McCree*, then-Justice Rehnquist explained that the Court was "far from persuaded * * * that the 'clearly erroneous' standard of Rule 52(a)" would apply to "'legislative' facts." 476 U.S. 162, 168 n.3 (1986) (citing *Dunagin*, 718 F.2d at 748 n.8).

b. It makes no difference that claim construction often involves scientific principles or terms of art. *Contra* Teva Br. 26-28. Factual questions about background scientific principles or the meaning of terms of art and the like are precisely the type of facts that transcend the particular dispute between the parties and are relevant "to legal reasoning and the lawmaking process"—i.e., defining the scope of the grant and what the public may lawfully do. Fed. R. Evid. 201 advisory comm. notes (1972).

Teva suggests that claim construction necessarily involves adjudicative factual issues because a patent is interpreted from the viewpoint of a skilled artisan. Teva Br. 26, 31. But the "person of ordinary skill in the art at the time of invention" is not an actual person; the "hypothetical person" of ordinary skill is "an imaginary being possessing 'ordinary skill in the art' created by Congress to provide a *standard of patentability*." *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1454 (Fed. Cir. 1984) (emphasis added); 35 U.S.C. § 112, ¶ 1 (establishing

"person skilled in the art" standard). As the standard of patentability, that legal fiction merely poses the *legal* question to be answered.

Thus, when a court interprets a patent, it looks through the eyes of this imaginary person working in the field. To do so, it may consult sources to learn about background scientific principles or the meaning of terms of art, just as this Court consults sources from the relevant time period to construe statutes. *E.g.*, *Perrin*, 444 U.S. at 42. As the government notes, courts "may need to receive additional evidence, such as expert testimony or scientific articles, in order to understand the relevant science and the technical terms used in the patent claims, specification, and prosecution history," and this evidence may give rise to "disputes about the accepted meaning in the relevant industry of a term found in a claim, or about the type of data that can be gleaned from a scientific experiment." US Br. 14.

But none of these factual issues in claim construction is unique to the dispute between the parties. They concern only the meaning—and therefore the legal scope—of the patent grant. Thus, scientific or not, they involve legislative facts just like those this Court routinely considers without deference. *See DePierre v. United States*, 131 S. Ct. 2225, 2232 (2011) (examining scientific and medical literature on use of the term "cocaine"); *Utah v. Evans*, 536 U.S. 452, 467 (2002) (explaining that "statutory phrase" uses "a term of art with a technical meaning" and "the technical literature, which we have consequently

examined," helps resolve the meaning (citing *Corning Glass Works v. Brennan*, 417 U.S. 188, 201 (1974))); *supra* pp. 24-25.

This is essentially the same point this Court made in *Brown v. Piper*, 91 U.S. 37 (1875). The Court explained that background knowledge in patent cases, even within a particular scientific field, does not require the type of "private and special facts" normally committed to a court of equity or a jury at law. *Id.* at 42. Rather, courts can resolve questions of law such as claim construction by reference to "whatever is generally known within the limits of their jurisdiction," which "extends to such matters of science as are involved in the cases brought before [them]." *Ibid.*; *see Terhune v. Phillips*, 99 U.S. 592, 593 (1879) (applying *Brown*).

Accordingly, because background scientific principles are merely legal tools to construe the scope of the patent claim, all aspects of claim construction are "purely legal" and properly reviewed de novo. *Markman*, 517 U.S. at 391.

3. *The Functional Advantages of Appellate Courts Support De Novo Review.*

This Court's general approach to deciding the applicability of plenary review confirms that de novo review follows from *Markman*. This Court generally looks to the question posed by *Miller v. Fenton*: whether one judicial actor is better positioned than another to resolve the dispute. *See, e.g.*, *Salve Regina Coll. v. Russell*, 499 U.S. 225, 233 (1991) (relying on

Miller in deciding whether to defer to a district court's interpretation of state law); *Cooter & Gell v. Hartmarx Corp.*, 496 U.S. 384, 403 (1990) (same with respect to Rule 11). Although Teva contends that factfinders are better positioned to decide claim construction issues (Teva Br. 19-24), the *Markman* Court already addressed *Miller*'s considerations and concluded otherwise. *Markman*, 517 U.S. at 388-91.

Because claim construction involves delineating the legal boundaries of a federal grant, the *Markman* Court concluded that the overriding consideration is which judicial actor can best produce the "'proper interpretation'" of the patent. *Id.* at 388-89 (quoting *Parker v. Hulme*, 18 F. Cas. 1138, 1140 (C.C.E.D. Pa. 1849)). The Court recognized that credibility judgments—the stock-in-trade of trial courts—thus "are much less significant than a trained ability to evaluate the testimony in relation to the overall structure of the patent." *Id.* at 390.

Similarly, a district court's ability to amass evidence and develop a record, *cf.* Teva Br. 24, is far less significant than an appellate court's ability to derive the correct legal principle—the meaning of the patent. As this Court has emphasized, "[c]ourts of appeals * * * are structurally suited to the collaborative juridical process that promotes decisional accuracy." *Salve Regina*, 499 U.S. at 232. Of course, the Federal Circuit is particularly well suited to this task because its judges review hundreds of patent claims every year. By contrast, most district court judges typically

hear far fewer patent cases as part of much more general dockets.

Appellate courts are also better equipped to derive the proper interpretation of a patent because claim construction does not focus on evidence outside the patent; it is a "sophisticated analysis of the whole document"—the claims, specification, and prosecution history (collectively, "intrinsic evidence"). *Markman*, 517 U.S. at 389-90 (focusing on "patent's internal coherence"); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314-17 (Fed. Cir. 2005) (en banc) (establishing framework for claim construction that focuses on intrinsic evidence). Although background technical or scientific evidence may be useful interpretive aids that, like dictionaries, help judges translate a patent's intrinsic evidence into terminology that judges more readily understand, such tools do not determine the legal import of the patent documents. As the Court put it long ago, "expert evidence" may aid a court "in understanding *not* what the instruments mean but what they actually say." *U.S. Indus. Chems., Inc. v. Carbide & Carbon Chems. Corp.*, 315 U.S. 668, 678 (1942) (emphasis added) (addressing validity of reissued patent).

In short, claim construction requires establishing the legal reach of the patent based on the instrument itself and the public record of its issuance. The Federal Circuit is better positioned to perform that function than district judges.

B. This Court's Pre-*Markman* Cases Support De Novo Review.

De novo review of all aspects of claim construction is consistent with this Court's historical practice. The Court has exercised such independent review in a long line of cases without suggesting that it owed any deference to trial court determinations, even when the trial court had considered extrinsic evidence such as expert and inventor testimony. *See, e.g.*, *Loom Co. v. Higgins*, 105 U.S. 580, 584-87 (1882) (independently considering evidence and settling the proper construction of the patent); *Tilghman v. Proctor*, 102 U.S. 707, 729-31 (1880) (same); *Winans*, 56 U.S. at 339 (giving no indication of deference to district court and reversing based in part on "what appears on the face of the specification, *and was testified to by experts at the trial as correct*" (emphasis added)); *Coupe v. Royer*, 155 U.S. 565, 576 (1895) (reversing based in part on Court's independent review of the inventor's testimony).

The Court's practice of independently reviewing all aspects of claim construction extended to cases—like this one—in which patent claims were challenged as indefinite. *See, e.g.*, *United Carbon*, 317 U.S. at 232-36 (independently searching the record, including considerable testimony, to determine "the clearest exposition of the significance which the terms employed in the claims had for those skilled in the art"); *General Electric*, 304 U.S. at 370-74 (holding claims indefinite with no apparent deference to lower court's reliance on live testimony); *see General Elec. Co.*

v. Wabash Appliance Corp., 17 F. Supp. 901, 904 (E.D.N.Y. 1937).

For instance, in *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923), this Court considered whether claims to an improved paper-making machine were indefinite. Teva repeatedly references *Eibel* for the proposition that expert testimony is often considered in indefiniteness disputes. Teva Br. 29-30, 44. But what Teva fails to mention, and what the opinion makes clear, is that the Court engaged in an independent and "thorough examination of the whole voluminous record." *Eibel*, 261 U.S. at 53. Nowhere did the Court suggest it gave any deference to the trial court's assessment of that evidence.

The government brushes aside this Court's historical practice on the ground that the early decisions did not suggest that the lower courts had made erroneous factual findings. US Br. 20 n.2. But only if the Court had considered itself bound to defer would it have felt the need to identify any finding as clearly erroneous. Here, as in other contexts, this Court's long practice of reviewing claim-construction rulings without "expressly deferr[ing] to the trial court's determination" supports de novo review. *Ornelas v. United States*, 517 U.S. 690, 697 (1996).

C. Standards Of Review Used In Other Areas Do Not Warrant Departing From De Novo Review Of Claim Construction.

In an effort to show that subsidiary factual findings in claim construction should be subject to clear-error review, Teva and the government analogize to other areas of law. These analogies are inapposite.

1. Teva and the government contend that claim construction is like contract interpretation, which can involve findings based on parol evidence that are reviewed for clear error. *See* Teva Br. 33; US Br. 15. This comparison is flawed. Unlike claim construction, contract interpretation does not involve delineating a legal rule—what the public may lawfully do. *See supra* pp. 3-5. In contract cases, courts consider parol evidence in certain limited circumstances to understand the intent of the parties to the agreement—a purely adjudicative fact. *See, e.g.*, 11 Williston on Contracts § 30:2 (4th ed. 2014) ("[T]he avowed purpose and primary function of the court is to ascertain the intention of the parties."); Fed. R. Evid. 201 advisory comm. notes (1972).

In contrast, a patentee cannot resort to such subjective intent about what it meant by its claims, or to any other private meaning. Patents themselves must "particularly point[ ] out and distinctly claim[ ] the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2. No amount of extrinsic evidence can change the scope of a claimed

invention. *See, e.g.*, *U.S. Indus. Chems.*, 315 U.S. at 678 ("It is inadmissible to enlarge the scope of the original patent by recourse to expert testimony * * * ").[4]

2. Teva also suggests that claim construction is like interpretation of tariffs filed with the Interstate Commerce Commission in that both can give rise to subsidiary factual questions regarding whether a term carries "a specialized meaning in the industry." Teva Br. 32 (citing *Great N. Ry. Co. v. Merchants' Elevator Co.*, 259 U.S. 285 (1922); *Texas & Pac. Ry. Co. v. American Tie & Timber Co.*, 234 U.S. 138 (1914)).

Those decisions are inapposite. Both concerned whether cases had to be referred to the Commission under the doctrine of primary jurisdiction, which seeks to have an expert administrative agency decide certain issues "to produce better informed and uniform legal rulings." *Pharmaceutical Research & Mfrs. of Am. v. Walsh*, 538 U.S. 644, 673 (2003) (Breyer, J., concurring) (citing *United States v. Western Pac. R.R. Co.*, 352 U.S. 59, 63-65 (1956)). In *American Tie & Timber*, for example, the issue to be decided by the Commission was not just a disputed meaning of a term of art; it was the ultimate issue—

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[4] Contrary to Teva's suggestion, Teva Br. 33 n.18, this Court did not acknowledge in *Brown v. Huger*, 62 U.S. (21 How.) 305 (1859), that parol evidence could create a factual question in the interpretation of a land patent. That case did not involve any inquiry "into the testimony of witnesses." *Id.* at 321.

an administrative determination whether the tariff applied. *See American Tie & Timber*, 234 U.S. at 146 ("[I]t is equally clear that the controversy as to whether the lumber tariff included cross-ties was one primarily to be determined by the Commission in the exercise of its power concerning tariffs and the authority to regulate conferred upon it by the statute."); *see also Great N. Ry. Co.*, 259 U.S. at 293 (explaining that, unlike a "question of construction," cases like *American Tie & Timber* required a "question of fact" or "administrative judgment" to be determined by the Commission). Rather than have important legislative, administrative, or adjudicative issues resolved separately by a jury or district court in each case, the primary-jurisdiction doctrine centralizes decision-making in a single expert body. *Allnet Commc'n Serv., Inc. v. National Exch. Carrier Ass'n, Inc.*, 965 F.2d 1118, 1120 (D.C. Cir. 1992). The desired "uniformity can be secured only if its determination is left to the Commission." *Great N. Ry. Co.*, 259 U.S. at 291.[5]

To the extent these primary-jurisdiction decisions are relevant at all, they support de novo review of claim construction. The same rationale supporting reliance on a centralized, expert administrative

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[5] Although the Court in *Great Northern* stated that the question submitted to the Commission is one that would otherwise be submitted to a jury, 259 U.S. at 292, this Court concluded in *Markman* that no aspect of claim construction goes to a jury.

agency supports plenary Federal Circuit review of claim-construction issues. *See id.* at 292. As the *Markman* Court explained, "[i]t was just for the sake of such desirable uniformity that Congress created the Court of Appeals for the Federal Circuit as an exclusive appellate court for patent cases." 517 U.S. at 390 (citing H.R. Rep. No. 97-312, at 20-23 (1981)).

3. Teva and the government also analogize to other areas of patent law, such as obviousness and enablement, suggesting that inquiries arising in these contexts raise factual issues that warrant deference on appeal. Teva Br. 34-35; US Br. 20. These analogies also miss the mark.

Unlike claim construction, these inquiries do not define the precise scope of a legal grant—the line between unlawful infringement and lawful conduct. *Markman* held that no jury was required for claim construction because claim construction looks primarily inward, at the public record. 517 U.S. at 385-87. Any factual issues underlying claim construction are part of the legal inquiry, "subsumed within the necessarily sophisticated analysis" of the patent document itself. *Id.* at 389.

In contrast, these other doctrines principally look outward. They take the scope of the claim as already determined and then compare that scope to evidence outside the document itself. Indeed, *Markman* distinguished the factual issues related to anticipation on that ground, contrasting the "document interpretation" of claim construction from the question

"whether the physical objects produced by the patent were identical." *Id.* at 386. The same is true with enablement, obviousness, and the doctrine of equivalents. After there has been a predicate determination of claim scope, the inquiry turns outward to see what those of skill in the art knew at the time outside the patent and whether they could make the claimed invention based on that knowledge combined with the patent's teachings (for enablement), whether the invention was apparent from the prior art (for obviousness), and whether the accused product performs substantially the same function in substantially the same way to obtain the same result as the invention (for infringement under doctrine of equivalents). *See* 35 U.S.C. §§ 103, 112; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (obviousness); *Expanded Metal Co. v. Bradford*, 214 U.S. 366, 378-81 (1909) (enablement); *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950) (doctrine of equivalents).

This Court's rulings as to who decides these issues confirm the critical distinction. Unlike claim construction, juries, not judges, decide the factual issues underlying these other doctrines. *See Battin v. Taggert*, 58 U.S. (17 How.) 74, 85 (1854) (enablement: "[i]t was the right of the jury to determine, from the facts in the case"); *Bischoff v. Wethered*, 76 U.S. (9 Wall.) 812, 814 (1870) (anticipation: the identity of a prior invention with an asserted patent is "treated as a question of fact for the jury, and not as a question of law for the court"); *Wood v. Underhill*, 46 U.S. (5

How.) 1, 4-5 (1847) (written description: "the sufficiency of the description must, in general, be a question of fact to be determined by the jury"). These decisions accord with the general principle that "issues of fact are to be determined by the jury" in actions analogous to those at law. *Baltimore & Carolina Line, Inc. v. Redman*, 295 U.S. 654, 657 (1935).

To be sure, invalidity is the consequence if a claim is indefinite, and some of the doctrines Teva cites are also invalidity defenses. But the nature of the inquiry is quite different: indefiniteness is an issue of claim construction—a determination that the public record does not sufficiently inform those of skill in the art of the claim's meaning. As such, Section 112's definiteness requirement must be evaluated based on the claim language, specification, and prosecution history. *Nautilus*, 134 S. Ct. at 2128. It is those documents that must provide the public with "reasonable certainty" as to the scope of the claimed invention. *Id.* at 2129. The other defenses to which Teva attempts to analogize all start with the proposition that the claim can be construed and then test the scope of the construed claim against real world facts to determine whether the claim is anticipated, rendered obvious, or not enabled.

Indeed, the indefiniteness inquiry is especially deserving of plenary appellate review. The definiteness requirement "was inserted in the law for the purpose of relieving the courts from the duty of ascertaining the exact invention of the patentee by inference and conjecture, derived from a laborious

examination of previous inventions, and a comparison thereof with that claimed by him." *Keystone Bridge Co. v. Phoenix Iron Co.*, 95 U.S. 274, 278 (1877). An adjudicative factual predicate to definiteness would upend the requirement that "a patent must describe the exact scope of an invention and its manufacture to 'secure to [the patentee] all to which he is entitled, [and] to apprise the public of what is still open to them.'" *Markman*, 517 U.S. at 373 (quoting *McClain v. Ortmayer*, 141 U.S. 419, 424 (1891)).

D. Uniformity In The Treatment Of Each Patent Requires De Novo Review.

The need for uniformity "in the treatment of a given patent"—and the Federal Circuit's role in reviewing all patent cases—was critical to *Markman*'s conclusion that claim construction should be treated as purely legal. 517 U.S. at 390-91. These considerations are no less important today. *See, e.g.*, *American Piledriving Equip., Inc. v. Geoquip, Inc.*, 637 F.3d 1324, 1327 & n.1 (Fed. Cir. 2011) (identifying seven district court decisions construing three terms of the same patent, with "no two [courts] hav[ing] construed all three terms the same way").

1. Teva attempts to sidestep the value of uniformity in three ways. None is availing.

First, Teva objects that uniformity cannot be a "free-standing principle of appellate review" or else the Federal Circuit could "review *everything* de novo." Teva Br. 44. But Markman was not concerned with uniformity as a freestanding principle; rather, it

focused on the uniformity of the meaning of a particular patent claim. 517 U.S. at 390. As a federally granted right, each claim can have only one meaning.

Second, Teva suggests that uniformity cannot be achieved because claim construction and indefiniteness rest on "factual findings," which can lead to different outcomes. Teva Br. 46-47. That begs the question. If claim construction is purely legal, there will be no disparate factual findings.[6]

Finally, Teva touts the supposed benefits of preclusion principles and written district court opinions. Teva Br. 47-49. But *Markman* already found preclusion insufficient because "issue preclusion could not be asserted against new and independent infringement defendants." 517 U.S. at 391. If preclusion principles cannot ensure the needed uniformity, district court decisions certainly cannot do so, as they are not even binding on other judges within the same district. Instead, the *Markman* Court recognized that claim-construction rulings should be treated as binding legal precedent, rather than as resting on a factual issue that could be relitigated. *Ibid.* Applying *stare decisis* promotes "uniformity in the treatment of a given patent" and the public-notice function of patent claims. *Id.* at 390-91.

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[6] Contrary to Teva's assertion (Teva Br. 46), *Mendenhall v. Cedarapids, Inc.*, 5 F.3d 1557 (Fed. Cir. 1993), did not hold that a determination of indefiniteness is not binding in a second case. The Federal Circuit did not reach indefiniteness because it held the claim invalid for obviousness. *Id.* at 1563 n.5.

2. Teva also makes several policy arguments directed at the allegedly deleterious effects of the Federal Circuit's high reversal rate of claim-construction rulings. Teva Br. 48-53. To begin with, recent studies have shown that the Federal Circuit does not have an unusually high reversal rate for claim-construction rulings and also that de novo review is not the cause of most reversals. *Lighting Ballast*, 744 F.3d at 1290-91.

More importantly, as this Court explained in *Markman*, Congress chose to achieve uniformity of patents through the establishment of the Federal Circuit. 517 U.S. at 390. Congress has been aware of the Circuit's consistent practice during the past 20 years. S. Rep. No. 110-259, at 27 (2008) (discussing *Markman* and *Cybor* by name). Indeed, Congress has considered changes directed to the review of claim-construction rulings and nonetheless left the de novo standard untouched. *See id.* at 28; 152 Cong. Rec. S8831 (daily ed. Aug. 3, 2006) (statement of Sen. Orrin Hatch).

As this Court has recognized in similar contexts, such a history strongly counsels in favor of retaining the court's long-established practice. *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2252 (2011). In any event, "Congress can legislate the [standard of review] out of existence any time it chooses. The various policy arguments now made * * * are thus best addressed to Congress, not this Court." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997) (retaining the doctrine of equivalents).

Teva's assertion that de novo review discourages settlement, Teva Br. 52, is also a policy question for Congress. Moreover, Teva has it backwards. By deciding claim construction as a pure question of law, trial courts are able to resolve claim construction early in the case, before the substantial costs of full discovery. Early claim construction thus may "facilitate settlement" and "permit resolution, either in whole or in part, through dispositive motions." Manual for Complex Litigation (Fourth) § 33.223 (2004).

In sum, the Federal Circuit properly reviewed the district court's indefiniteness decision de novo. That mandates affirmance because Teva does not challenge the merits of the judgment under that standard.

II. EVEN IF NOT ALL ASPECTS OF CLAIM CONSTRUCTION ARE REVIEWED DE NOVO, THE OUTCOME HERE IS THE SAME.

Even if the Court concludes that there can be factual findings in claim construction warranting appellate deference, the Court should expressly apply that standard here and affirm the judgment.

The court of appeals correctly held the patent claims at issue indefinite because a critical claim term is conceded to be ambiguous on its face, the specification provides nothing to resolve the ambiguity, and the prosecution history compounds the ambiguity because Teva gave the PTO irreconcilable answers at two different times, each of which resulted

in the issuance of a patent with the same claim term and the same specification. That public record does not provide the notice required, even though it would have been simple for Teva to do so. *Nautilus*, 134 S. Ct. at 2129. That conclusion will be the same even if deference is accorded to factual findings, because the Federal Circuit did not disagree with anything that could plausibly be considered a factual finding.

A. Any "Facts" Must Be Limited To Principles Separate And Apart From The Patent And Prosecution History At Issue.

If there can be factual findings in claim construction at all, what is considered a "fact" must be carefully cabined. As the government observes, it is "essential to distinguish the district court's factual findings from its subsequent legal inferences," US Br. 26, because only the former would be entitled to clear-error review under Rule 52. Any "facts" should be limited to scientific principles or other issues whose truth is determined separate and apart from the particular patent asserted. Facts should not include attempts by paid experts to interpret the meaning of the public record at issue—the patent's claims, specification, drawings, and prosecution history. Otherwise the notice function of the patent will be severely undermined to the detriment of innovation and the purposes underlying the patent system.

1. All the reasons in Part I compel this boundary between fact and law. At the very least, *Markman* held that all "*interpretive* issues" are "purely

legal." 517 U.S. at 391 (emphasis added). *Markman* consistently described the task of discerning the meaning of a patent's claims and specification as a legal one. To the extent *Markman* suggested there could be "evidentiary underpinnings" in claim construction, it rightly expressed "doubt[ ]" that many cases would turn on credibility determinations. *Id.* at 389-90. And the only fact-like issues to which *Markman* alluded were background facts separate and apart from the patent at issue, such as "a question of meaning peculiar to a trade or profession." *Id.* at 389.

Other decisions by this Court support that attempts by paid experts to interpret the meaning of a patent and its prosecution history are not "facts." The Court has held that "[e]xperts may be examined as to the meaning of terms of art * * * but not as to the construction of written instruments." *Corning v. Burden*, 56 U.S. (15 How.) 252, 270 (1854); *Winans*, 62 U.S. at 101 ("[P]rofessors or mechanics cannot be received to prove to the court or jury what is the proper or legal construction of any instrument of writing."). In other words, while an expert's explanation of background scientific terms or principles separate and apart from the patent at issue could potentially lead to a factual finding, the expert's interpretation of the patent itself could not.

The two patent treatises relied on by the Court in *Markman* support this line. 517 U.S. at 387-88. As one explained, "'[w]here technical terms are used, or where the qualities of substances * * * or any similar

data necessary to the comprehension of the language of the patent are unknown to the judge, the testimony of witnesses may be received upon these subjects.'" *Id.* at 388 (quoting Robinson, *supra*, § 732, at 481-83). "'*But in the actual interpretation of the patent the court proceeds upon its own responsibility, as an arbiter of the law.*'" *Ibid.* (emphasis in *Markman*).

The reasons for drawing this line are sound. "Experience has shown that opposite opinions of persons professing to be experts may be obtained to any amount." *Winans*, 62 U.S. at 101. Opinions of paid experts "can suffer from bias that is not present" in the public record because "expert reports and testimony [are] generated at the time of and for the purpose of litigation." *Phillips*, 415 F.3d at 1318.

Indeed, if an expert's interpretation were a matter of "fact," that would cast grave doubt on *Markman*'s Seventh Amendment holding. That holding depended on the conclusion that any credibility determinations would be "subsumed within the necessarily sophisticated analysis of the whole document." *Markman*, 517 U.S. at 389. But if an expert's testimony regarding the meaning of the patent and its prosecution history were a fact, *Markman*'s premise would be undeniably false: the construction of patent claims would be "subsumed within" credibility determinations. *Every* claim-construction dispute would devolve into a trial with paid experts setting forth their competing opinions and explanations of the meaning of the patent claims, specification, and prosecution history—with the ultimate construction

turning on which expert the district court chose to "credit."

Thus, although a district court may draw its conclusions regarding the meaning of a patent and its prosecution history from a litigation expert's interpretation of that public record, the court's conclusions are nonetheless *legal* ones and thus reviewed de novo. *Highmark*, 134 S. Ct. at 1748. A patentee's attempt to use a litigation expert to cure its faulty claims and explain away the irreconcilable public record *it* created (as Teva tried to do here) does not create a "fact" entitled to appellate deference.

2. Teva does not clearly elucidate where it would draw the line between fact and law. At times, Teva's position seems consistent with the above boundary, suggesting that facts "lie outside the four corners of the patent and its prosecution history." *E.g.*, Teva Br. 27 ("the level of ordinary skill in the art at the relevant time"), 32 ("vocabulary, usage, and customs among the relevant community"), 43 ("the accepted meaning in the relevant scientific community at the relevant time"). To that extent, Teva shares common ground with the government, *e.g.*, US Br. 14, and respondents (if this Court rejects de novo review). As the government rightly observes, however, such background scientific principles "[o]ften" are "essentially uncontested." *Ibid.*

In other places, however, Teva suggests that "facts" include much more: a litigation expert's interpretation of the meaning of the patents and the

prosecution history at issue, including assumptions and inferences that the expert draws from that public record. *See, e.g.*, Teva Br. 20, 27-33. To the extent Teva relies on an analogy to contract principles for that proposition, Teva Br. 33, that analogy is inapt, for the reasons discussed above. *See supra* pp. 33-34. The question in claim construction is the scope of a legal grant by the government, binding against the public; not the meaning of a private agreement between the parties to the dispute. The meaning of that legal grant should not turn on a district court's choice between experts.

Teva cites *Ornelas* in contending that "inferences" are reviewed for clear error even when they relate to a legal inquiry that is reviewed de novo. Teva Br. 20. But the inferences there related to a purely factual inquiry: "the events which occurred leading up to the stop or search." *Ornelas*, 517 U.S. at 696-97. Such "background facts" included what could be inferred about traveling to Milwaukee in the winter or where the officer who performed the search believed narcotic traffickers tend to hide drugs in cars. *Id.* at 699-700. But whether there was probable cause to stop or search based on those facts was reviewed de novo—even though it was "a mixed question of law and fact." *Id.* at 696-97. If anything, *Ornelas* supports de novo review of the application of

background scientific facts to the patent and its prosecution history.[7]

Teva also suggests that all determinations based on extrinsic evidence are factual findings subject to Rule 52. *See, e.g.*, Teva Br. 27-29, 41-44. But just because evidence is "extrinsic" does not make all conclusions drawn from it "facts." This is particularly true with expert testimony which, as here, often includes not merely information about relevant background scientific principles, but also the expert's own interpretation of the public record at issue. While the former might be considered facts, the latter are legal conclusions that should be reviewed de novo. *See Winans*, 62 U.S. at 101; *Corning*, 56 U.S. at 270.

Finally, although the meaning of a patent claim (and whether its meaning is reasonably certain) is judged by a skilled-artisan standard, that does not mean that the inquiry is predominantly factual. *Contra* Teva Br. 29. As explained above, "the person of skill in the art" is a legal fiction that merely expresses a standard of patentability. *Supra* pp. 26-27. Teva's assertion that "the dominant inquiry will be a factual one" (Teva Br. 29) cannot be squared with *Markman*: what the patent claims mean (and whether the public record provides sufficient notice to

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[7] In *Anderson v. City of Bessemer City*, 470 U.S. 564, 574 (1985), which Teva also cites (*e.g.*, Teva Br. 22), any inferences were factual because (unlike here) the entire inquiry was factual, including the ultimate issue of intentional discrimination. 470 U.S. at 573.

construe them at all) is the *legal* inquiry at issue in claim construction and indefiniteness. 517 U.S. at 389; *Nautilus*, 134 S. Ct. at 2125.

3. The expert declarations that Teva submitted here illustrate the boundary between what could properly be considered a fact and what cannot.

In the paragraphs entitled "BACKGROUND POLYPEPTIDE AND MOLECULAR WEIGHT PRIMER," Grant mostly opined about scientific principles that he believed to be true in general, wholly separate and apart from Teva's patents and their prosecution history. For example, Grant described how the process of SEC works in general, and the three types of average molecular weight measurements that can be obtained from that process. Pet. App. 106a-07a ¶39. Insofar as this Court decides there can be "facts" in claim construction, these types of background principles might lead to a factual finding.

Teva's declarations, however, went well beyond principles that Grant asserted were true in general. Nearly three dozen paragraphs were entitled "CLAIM CONSTRUCTION" and expressly stated: "[i]n the paragraphs that follow, I set forth *my opinion as to the proper interpretation of phrases or terms in the claims of the patents-in-suit*." Pet. App. 118a-36a at 118a ¶54 (emphasis added); *accord* J.A. 129a-48a at 129a ¶44. In these "Claim Construction" paragraphs, Grant made assumptions and drew conclusions for purposes of litigation from the common specification and prosecution history to support his opinion about

the meaning of the claims. *E.g.*, Pet. App. 125a (opining about what the absence of a description of calculations in Teva's patents' specification "would have indicated").

These assumptions and conclusions were not "facts"; they were legal interpretations of the public record. As the government explains, "the correct legal inferences to be drawn from the patent's language and prosecution history" are legal issues reviewed de novo. US Br. 23; *see* US Br. 27.

In construing the term "average molecular weight" to mean "peak," the district court drew the same legal conclusions as Grant, purporting to make findings by "crediting" and "accepting" Grant's interpretation. Pet. App. 44a, 49a-50a. While a district court may consider such opinions, that does not transform its conclusions into "factual findings." Rather, "a district court's ultimate construction of a patent claim remains legal even if the court purports to credit an expert witness's testimony that a skilled artisan would understand the claim in a particular way." US Br. 23.

Applying this line between fact and law will not result in "relitigat[ing] the facts on appeal." Teva Br. 21. It will properly cabin "facts" to principles that are true (or not) in the world generally, and properly treat all interpretations of the public record as legal, as *Markman* (at the very least) requires. 517 U.S. at 391.

B. The Federal Circuit Overturned No Factual Findings In Correctly Holding The Claims Indefinite.

As the government rightly recognizes, applying this line between fact and law requires the same outcome here. US Br. 26. Reviewing the public record Teva created, the Federal Circuit correctly held Teva's "molecular weight" claims indefinite, even under the Circuit's now-rejected, overly strict "insolubly ambiguous" standard. Pet. App. 6a-10a.

The court of appeals noted the significant uncontested points. It is "undisputed" that the claims are ambiguous on their face "because their plain language does not indicate which average molecular weight measure is intended." Pet. App. 8a. It is undisputed that the term "average molecular weight" "has no 'ordinary and customary meaning'" to persons of skill in the art. Pet. App. 42a. And it is undisputed that it is critical to know which one of the several different measures is intended to understand the limits of what is claimed and what remains open to the public. Pet. App. 4a-5a.

Teva contends the Federal Circuit overturned three factual findings. Teva Br. 13-14, 54-58. But the court did not reject any determination that could properly be considered "factual." Rather, engaging in "*de novo* review of the district court's indefiniteness holding," Pet. App. 10a, the court reached a different legal conclusion, Pet. App. 6a-10a. That conclusion is correct.

1. The Court of Appeals Accepted the Only Plausible Fact Regarding the Prosecution History.

The Federal Circuit correctly concluded that Teva's irreconcilable answers to the PTO regarding the meaning of molecular weight rendered the ambiguity in the claims "insoluble." Pet. App. 9a. In so holding, the court accepted the only plausible factual finding—one of Teva's answers contained a scientifically incorrect explanation. Pet. App. 8a.

a. Twice during prosecution of this family of patents, the PTO reviewed the common specification and concluded that, without more information, Teva's proposed "molecular weight" claims were indefinite. Each time, Teva provided a different answer; and based on each answer, Teva was issued a patent with the same specification and the same claim term. *See supra* p. 7.

Respondents contended below that these plainly contradictory statements—that the same "molecular weight" term has two fundamentally different meanings—confirmed the patents were indefinite. The district court disagreed, concluding that, because Teva's explanation for its "weight" answer was scientifically "incorrect," a skilled artisan would disregard that answer and instead rely on Teva's "peak" answer. Pet. App. 52a. Teva contends this analysis is a finding of "fact" to which the Federal Circuit should have deferred. Teva Br. 57-58.

As the government explains, however, only the district court's determination that Teva's explanation was scientifically inaccurate could properly be considered a factual finding. US Br. 27-28. The types of weight to which the "kilodalton" unit can refer "concern[] scientific principles and understandings as they exist in the field, outside the patent." US Br. 27. That scientific principle, however, has never been in dispute.

The conclusion the district court drew from that uncontested principle is a legal conclusion. Indeed, in ruling that the "weight" answer should be disregarded, the district court relied on Grant's self-described "Claim Construction," which was based on his own interpretation of the patent record as a whole. Pet. App. 52a (citing J.A. 140a ¶64); *see* J.A. 140a ¶¶64-65. That the district court agreed with Grant's interpretation (Pet. App. 52a (relying on J.A. 140a ¶64)) does not transform that interpretation into a factual finding. *Corning*, 56 U.S. at 270; *Winans*, 62 U.S. at 101; *see* US Br. 28.

b. On review, the Federal Circuit correctly reached a different legal conclusion.

The court accepted that Teva's *explanation* for one of its answers was "an evident scientific error." Pet. App. 8a.[8] Nevertheless, the court correctly focused

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[8] Teva wrongly faults the Federal Circuit for "never even acknowledg[ing] it." Teva Br. 58; *cf.* US Br. 28 (incorrectly stating the court ruled "without mentioning * * * the inaccuracy").

on Teva's two irreconcilable *answers* to the PTO, each of which resulted in issuance of a patent. Pet. App. 9a. As the Federal Circuit explained: "[t]he only basis upon which the Examiner could have agreed that the '539 patent claims were not indefinite was that 'molecular weight' means M_p. In contrast, the only basis for the Examiner's withdrawal of the indefiniteness rejection of the '847 patent claims was that the same term means M_w." *Ibid.* "Teva's two definitions cannot be reconciled" and thus "render the ambiguity insoluble." *Ibid.*

That is a purely legal analysis—an interpretation of the patent in light of its prosecution history. As the government explains, "the relative weight that a skilled artisan *interpreting the patent claims* would accord each prosecution-history statement in light of the fact that one of the statements contained a scientific inaccuracy" is a legal conclusion. US Br. 28 (emphasis by US).

And the Federal Circuit's legal conclusion is correct. Whatever Teva's rationale may have been, the Examiner accepted Teva's answer that "*weight* average molecular weight" was the meaning of the otherwise ambiguous "molecular weight" claims and granted a patent because of that answer. *See, e.g.*, *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985). Teva cannot use a litigation expert to negate a now-inconvenient answer to the PTO, because without that answer Teva would not have obtained its patent. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736 (2002).

Moreover, the "scientific error" went only to Teva's explanation for its failure to specify the type of molecular weight, not to its answer about which measure the claims used. Because the precise "average molecular weight" was key to these claims, a skilled artisan would have no reason to doubt that Teva knew which measure it intended, and thus no reason to doubt the "weight" part of Teva's answer. To take Teva's example (Teva Br. 58), if "degrees" were key to an invention, and the applicant told the PTO the term meant "Celsius," a skilled artisan would believe that to be the measure, even if the applicant's excuse for not previously specifying it had been scientifically inaccurate. *See Springs Window Fashions LP v. Novo Indus., L.P.*, 323 F.3d 989, 996 (Fed. Cir. 2003) ("A reasonable competitor would have believed that the applicant's disclaiming statements were not a mere mistake.").

c. Attempting to avoid its irreconcilable representations to the PTO, Teva argues for the first time that this prosecution history is irrelevant to the '808 patent, because both answers were made after that patent issued. Teva Br. 57. Even if that substantive patent-law argument were within the question presented (it is not), it does not help Teva.

All the patents—including the '808 patent—trace back to the same patent application, share the same specification, and contain the same "molecular weight" claim term. A person of ordinary skill in the art thus would look to the prosecution history of the entire family of patents to discern the scope of the claims.

Microsoft Corp. v. Multi-Tech Sys., Inc., 357 F.3d 1340, 1350 (Fed. Cir. 2004); *see Nautilus*, 134 S. Ct. at 2128.

Indeed, while the other patents remained unexpired, Teva consistently argued that its "peak" answer applied to *all* the claims in *all* the asserted patents, including the '808 claim. In the Federal Circuit, Teva contended that "the prosecution history of one patent in a chain may be used to construe the same term in both earlier and later issued related patents with the same specification." Teva CAFC Br. 46 (citing *Microsoft*, 357 F.3d at 1350). In district court, Teva's expert repeatedly relied on the prosecution history answer of "peak" to bolster his interpretation of all the patents. *E.g.*, J.A. 140a, 187a, 194a, 206a-07a. It is too late for Teva to abandon that argument now.

2. The Court of Appeals Accepted the Identified Factual Findings About the SEC Method.

Turning to the specification, the Federal Circuit correctly concluded that "[t]he specification does not resolve the ambiguity" created by the claims and the prosecution history. Pet. App. 9a-10a. As the government explains, in reaching that conclusion, the court "did not overturn or implicitly reject the district court's factual findings concerning SEC." US Br. 29.

a. The district court concluded that "Mp can be read from the chromatogram generated by SEC without any 'further calculation' and would be understood by a person of ordinary skill in the art to be the presumed meaning of [average molecular weight] in the context of the patents-in-suit." Pet. App. 43a (citing J.A. 138a ¶61). Teva contends that is a "fact." Teva Br. 56-57. But again, only the first part of the district court's statement—that "Mp can be read from the chromatogram generated by SEC without any 'further calculation'"—could be considered a "fact." US Br. 29-30.

As Grant explained, the data generated by the SEC method is plotted on a graph, called a chromatogram. J.A. 126a-28a ¶41. By running "standards" of known molecular weight through the same SEC column, a calibration curve can be created. J.A. 128a-29a ¶42. "With a chromatogram and a proper calibration curve, the peak average molecular weight * * * can be read without any further calculation." J.A. 129a ¶43. Respondents did not dispute these scientific principles. Indeed, there was no dispute as to the various types of weight the SEC method can measure in general. As the district court noted, SEC "can also provide Mw and Mn" if further calculations are performed. Pet. App. 48a.

But the district court's "presumption" about what a method of measurement means "*in the context of the patents-in-suit*," Pet. App. 43a (emphasis added), is a legal conclusion, *accord* US Br. 30-31. It is not a scientific principle separate and apart from these

patents. *See Corning*, 56 U.S. at 270; *Winans*, 62 U.S. at 101; *accord* US Br. 31. The district court was embracing Grant's "Claim Construction" analysis, based on what was and was not in the public record. J.A. 138a ¶61. Indeed, Grant expressly did *not* assert that "peak" was the "default meaning to a person of skill in the art" of the term "average molecular weight." J.A. 187a. Grant pointed instead to the prosecution history. *Ibid.* Although the district court purported to "credit" Grant's interpretation, Pet. App. 49a (citing Pet. App. 125a ¶70), "[t]hat conclusion, though phrased as a credibility finding, is a legal determination," US Br. 30.

b. The Federal Circuit disagreed only with the district court's legal conclusion. The court accepted that M_p can be "read directly from a plot of SEC data," whereas "some calculations" are required to obtain M_n and M_w. Pet. App. 10a. But it emphasized that "SEC does not exclusively provide M_p—both M_n and M_w can also be obtained from the data generated by the SEC method." *Ibid.* Given those undisputed scientific principles, the Federal Circuit concluded that the mere reference to the SEC method does not resolve the claims' ambiguity. *Ibid.*

As the government explains, that is a legal conclusion. US Br. 31. And that conclusion is correct. The specification contains no mention of the intended measure. The fact that, with a chromatogram and a "proper calibration curve" in place, the peak molecular weight "can be read directly off the calibration

curve," J.A. 128a-29a ¶¶42-43, does not establish the claims mean peak. The specification contains no calibration curve. J.A. 1143a-45a. Nor does it suggest that further calculations would not be needed. *Ibid.* The parties agreed that the relevant skill in the art here was very high, Pet. App. 94a, and that all three types of average molecular weight could be obtained using the SEC method, Pet. App. 106a-07a; J.A. 125a ¶39, 158a ¶37. Indeed, the PTO Examiner, "a subject-matter expert," Teva Br. 29, reviewed the specification and twice rejected the claims for indefiniteness despite the reference to SEC. *See supra* p. 7.

The Federal Circuit thus correctly concluded that the mere reference to SEC failed to "provide sufficient clues to discern" which measure the claims encompassed. *See Honeywell Int'l, Inc. v. ITC*, 341 F.3d 1332, 1340-41 (Fed. Cir. 2003) (holding claim indefinite where patent failed to specify which of four methods was intended for critical term).

3. *The Federal Circuit's Conclusion Regarding Figure 1 Is Fully Consistent with the Slight Shift Expected by Teva's Expert.*

The Federal Circuit also correctly concluded that Figure 1 did not resolve the claims' ambiguity.

a. It is undisputed that the "peaks" of the Figure's three curves (as measured by the horizontal axis) do not match the values for average molecular weight in the legend:

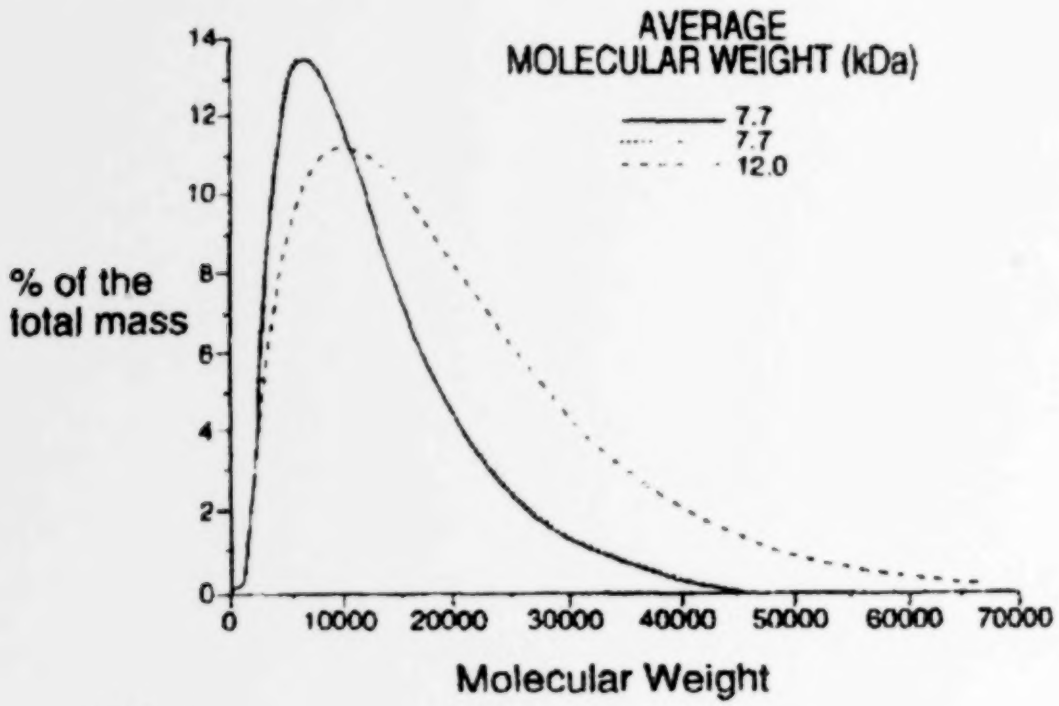

FIG. 1

J.A. 1141a. For the two overlapping curves identified by the legend as having an average molecular weight of 7.7 kDa, Grant "measured the peak to be at 6.8 kDa." J.A. 138a-39a ¶62. For those same curves, Grant calculated the "weight" average molecular weight to be 8.3 to 8.5 kDa. J.A. 310a.[9]

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[9] Teva notes that Mylan's expert, Chang Ryu, calculated M_w in Figure 1 to be 12.9 kDa. Teva Br. 56 n.34. But neither the district court nor the Federal Circuit relied on Ryu's interpretation of the Figure. *Contra* Teva Br. 55.

Relying on Grant, the district court determined that a person of skill in the art would understand that the process of creating molecular weight distribution curves (such as in Figure 1) from the data generated by an SEC chromatogram "'would likely cause the peak on each curve to shift slightly'" from where the peak was on the chromatogram. Pet. App. 45a (quoting J.A. 138a-39a ¶62); *see* Pet. App. 111a-18a ¶¶44-53 (explaining the shift). In so concluding, the district court implicitly rejected the view of Mylan's expert that the creation of such a graph would not cause a shift. Teva Br. 55; US Br. 31-32. As the government explains, that determination could be considered a factual finding because it involves a scientific principle separate and apart from these particular patents. US Br. 31.

But the district court's further reliance on Grant's interpretation of Figure 1 in these particular patents could lead only to a legal conclusion reviewed de novo. In his self-described "Claim Construction," Grant used his own calculation of the peaks in the Figure's curves to opine: "[t]he peaks of the curves are close to those numbers [in the Figure's legend] which would support the assumption that the numbers in the legend were peak molecular weights." J.A. 138a ¶62. That was the opinion the district court purported to "credit" and "accept" when it concluded that "the fact that the peaks in Figure 1 do not match the listed [average molecular weights] precisely would not dissuade a person of ordinary skill in the art from concluding that [average molecular weight] refers to

Mp in the context of the patents-in-suit." Pet. App. 49a (citing J.A. 138a-39a ¶62).

b. In holding these patents indefinite, the Federal Circuit did not reject that converting data to such distribution curves "would likely cause the peak on each curve to shift slightly." Pet. App. 45a.

Rather, the court noted the undisputed contention that "the peaks of the curves in Figure 1 do not correspond to the values denoted as 'average molecular weight' in the figure's legend." Pet. App. 10a. Then, citing *Grant's* calculations of the M_n of the curves in Figure 1, the court observed that the legend's "7.7 kDa value is closer to the M_n than to the M_p of the corresponding batch." Pet. App. 10a (citing J.A. 310a). Given that neither type of measure (as calculated by Grant from the Figure's curves) matched the legend, but both were close to the values in the legend, the Federal Circuit reasoned that this "makes it difficult to conclude [from Figure 1] that M_p is the intended measure." *Ibid.*

That interpretation of the patent is a legal analysis. *See Markman*, 517 U.S. at 389; *Corning*, 56 U.S. at 270; *Winans*, 62 U.S. at 101. The conclusion is completely consistent with an expectation that the curves would have "shift[ed] slightly" in the creation of the graph. *Contra* US Br. 32. And the conclusion is correct.

Grant's interpretation (and hence the district court's conclusion) hinged on the peaks at 6.8 kDa in the overlapping curves being "close" enough to the

"corresponding" 7.7 kDa in the legend to be within an unspecified "margin of error" due to the expected slight shift. Pet. App. 126a-27a ¶72. In other words, Grant believed that the peaks in the curves represented the M_p, and because he expected each peak to have "shift[ed] slightly" due to the transformation of the data from the chromatogram, he was willing to assume that the legend reported the value for that batch's M_p. *Ibid.* Grant explained that the magnitude of the expected shift in such a graph, and whether it would shift right or left, would depend on the underlying data. Pet. App. 113a ¶46, 118a ¶53. But Grant conceded that he could not determine the shift's magnitude or direction in Figure 1 because he did not have, and did not ask Teva for, the underlying "primary data" (which were not in the public record). J.A. 196a-97a.

However, given that Grant was willing to assume that the peaks at 6.8 kDa showed the M_p of the batches corresponding to the 7.7 kDa values in the legend, Grant's expected margin of error was necessarily a shift in the overlapping curves of at least 0.9 kDa in either direction. Yet Grant's *own* calculation of the M_w of those curves was likewise within that same margin of error; indeed, as the Federal Circuit noted, Grant's M_w calculation was "closer" to the legend's 7.7 kDa value. Pet. App. 10a (citing J.A. 310a). Grant calculated the M_w of those curves to be 8.3 to 8.5 kDa (J.A. 310a)—a 0.6 to 0.8 difference from the 7.7 kDa values in the legend. Accordingly, *either* measure, M_w

or M_p, is fully consistent with the expected slight shift in the curves.

That conclusion is not the result of the Federal Circuit "eyeball[ing] its way to its own decision" or "accepting the view of Mylan's expert" that there would be no shift. Teva Br. 55. Indeed, the Federal Circuit did not mention that testimony from Mylan's expert. Rather, without disputing the shift, the court relied on *Teva's* expert's own calculations and opinions about the meaning of Figure 1 to conclude that the Figure could not resolve the facial ambiguity of Teva's patent claims.

In any event, as the government acknowledges, any supposed error (and there was none) "likely did not affect [the Federal Circuit's] ultimate conclusion." US Br. 32-33. "Figure 1's failure to illustrate M_p values" was merely "an *additional* reason" the court of appeals held the patents indefinite. US Br. 33 (emphasis by US). Indeed, even the district court ultimately concluded only that the Figure "would not *dissuade* a person of ordinary skill in the art from concluding" that the "molecular weight" term refers to "peak," Pet. App. 49a (emphasis added)—not that the Figure eliminated the claims' ambiguity.

C. This Court Should Apply Any New Standard To Provide Guidance To Lower Courts.

If this Court concludes claim construction can include both findings of fact and conclusions of law, it should apply that distinction here to provide

concrete guidance as to the line between fact and law—a line this Court has elsewhere called "elusive" at best. *Miller*, 474 U.S. at 113. Guidance will be critical because claim-construction disputes occur in virtually every patent case. As the en banc Federal Circuit observed, "[d]isentangling arguably factual aspects * * * is a task ripe for lengthy peripheral litigation." *Lighting Ballast*, 744 F.3d at 1284.

This Court often applies new legal standards in patent cases. *See, e.g.*, *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011) (applying different inducement standard while affirming judgment); *KSR*, 550 U.S. at 422 (applying obviousness standard to invalidate patent). The Court is particularly well-positioned to do so here, where the standard is one of appellate review and the line between fact and law is itself a question of law.

Finally, as the government notes, Teva's only remaining patent at issue expires in September 2015, before any remand likely could be decided. US Br. 33 n.5. Although respondents can market upon FDA approval under threat of infringement liability, they should not face that risk any longer than necessary. Accordingly, the Court should fully resolve this case now so that patients can benefit from competition unimpeded by Teva's invalid patent.

CONCLUSION

The judgment should be affirmed.

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v.

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Respondents.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

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RULE 29.6 STATEMENT

The disclosure statement included in the opening brief remains accurate.

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OTHER AUTHORITIES:

Peter S. Menell, et al., *Patent Case Management Guide* § 5.3.2.5 (Fed. Judicial Ctr. 2009) 14

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REPLY BRIEF FOR PETITIONERS

A district court's task is to read a patent as a skilled artisan would. "What seems clear to a judge may read otherwise to a skilled designer." *In re Mahurkar Double Lumen Hemodialysis Catheter Patent Litig.*, 831 F Supp. 1354, 1359 (N.D. Ill. 1993) (Easterbrook, J.), *aff'd on other grounds*, 71 F.3d 1573 (Fed. Cir. 1995). And discerning the skilled designer's perspective will often require the generalist judge to take evidence and to resolve factual disputes between the parties. In any other context, in any other court of appeals, the district court's resolution of a scientific disagreement or dispute over specialized terminology would be presumed correct. Nothing in patent law justifies the Federal Circuit's refusal to follow that same principle.

De novo review has produced too many cases like this one, in which the Federal Circuit second-guesses the district court on fundamentally factual questions. This Court should end that experiment.

I. Defining The Scientific Techniques And Terminology In A Patent May Require District Courts To Find Classic Adjudicative Facts.

A. Except For The Federal Circuit, Appellate Courts Defer To District Courts' Findings On The "Fact" Part Of A Mixed Question Of Law And Fact.

The Federal Circuit, respondents, and their *amici* all argue that because the *end product* of claim con-

struction is reviewed *de novo*, supporting facts must be reviewed *de novo* too. But facts do not dissolve into law that way. To the contrary, Rule 52(a)(6) applies equally to "'subsidiary' facts" and "'ultimate' " facts. *Pullman-Standard v. Swint*, 456 U.S. 273, 287 (1982). In every other area of law, including the interpretation of other written instruments, the facts supporting a legal conclusion are reviewed deferentially. Patent law is no different.

At least once before, this Court sharply cautioned the Federal Circuit to follow this rule and defer to *subsidiary* factual findings. Whether a patent is obvious in light of the prior art is a legal question. But a court can answer that legal question only against the "background" set by "*factual* inquiries" that overlap with those in claim construction: what is the level of ordinary skill in the art and what would a skilled artisan know of the prior art? *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) (emphasis added). When the Federal Circuit reversed a holding of obviousness without explaining why the underlying factual findings were clearly erroneous, this Court readily corrected that error: even though "the ultimate question of obviousness" is not "a question of fact subject to Rule 52(a), the *subsidiary* determinations of the District Court, at the least, ought to be subject to the Rule." *Dennison Mfg. Co v. Panduit Corp.*, 475 U.S. 809, 811 (1986) (per curiam) (emphasis added). Respondents offer no response to this point; they do not even cite *Graham* or *Dennison*, which directly refute their contention that patent law permits factual findings only when the ultimate question is factual. *See* Resp. Br. 37-38.

Even in the standard-of-review case on which respondents chiefly rely, *Miller v. Fenton*, 474 U.S. 104 (1985), this Court carefully reiterated that facts receive deferential review. In *Miller*, the Court considered whether the habeas statute's presumption of correctness for "factual issues" applies to a state court's conclusion that a confession was voluntary. While the Court concluded that the "ultimate issue of 'voluntariness' " is not a factual finding, it carefully noted that within the voluntariness question lie "subsidiary questions" of historical fact, which may well involve the resolution of conflicting testimony. *Id.* at 117. Those questions do not lose their factual character just because they are subsidiary, and a trial court's answers are reviewed deferentially, not *de novo*. *See id.*; *see, e.g.*, *United States v. Pelletier*, 469 F.3d 194, 201 (1st Cir. 2006) (deferring to findings of historical fact, which in turn compelled the legal conclusion that statements were voluntary); *United States v. Navarro*, 90 F.3d 1245, 1258 (7th Cir. 1996) (same).

That is simply standard practice. In a host of contexts, the Court has held that while an ultimate issue may be a mixed question subject to *de novo* review, the appellate court must accept the facts found by the district court, absent clear error. *See, e.g.*, *Knowles v. Mirzayance*, 556 U.S. 111, 126 (2009) (ineffective assistance of counsel); *Thompson v. Keohane*, 516 U.S. 99, 112 (1995) (custody); Pet. Br. 20.

The Federal Circuit bemoaned the supposed difficulty of "[d]isentangling arguably factual aspects" of claim construction. *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1284 (Fed. Cir. 2014) (en banc). But appellate courts *regu-*

larly separate law from facts. They even did so in patent cases before the Federal Circuit was created. *Harries v. Air King Prods. Co.*, 183 F.2d 158, 164 (2d Cir. 1950) (L. Hand, J.); Pet. Br. 45. There is no reason why the Federal Circuit cannot do the same.

B. There Is No Claim-Construction Exception To Rule 52.

Respondents' various attempts to remove patent-related factfinding from the scope of Rule 52 are unavailing.

First and foremost, patents are scientific documents written for scientists—persons skilled in the relevant art. Courts accordingly must interpret a patent through the eyes of a skilled artisan. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2128 (2014). Respondents' key analogy between patents and statutes founders on that basic principle. Statutes are written for the same general audience, including judges. Patents and many other written instruments are not; each is written for an interpretive community that shares a "mass of previous knowledge and nomenclature" that is *not* "written out in the patent," but is just as much a part of the patent as if it were. *Loom Co. v. Higgins*, 105 U.S. 580, 585-86 (1881).

That interpretive community *does not include* the judge. Before construing such a document, the judge must learn what the document's intended readership already knows. This Court recognized in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), that that part of interpretation is factual in nature. And the judge acquires those facts not through free-

wheeling "legislative factfinding," but through the evidentiary process.

1. *Markman* Does Not Turn Claim-Construction Facts Into Law.

Markman did not hold that there "were no subsidiary 'factual' issues" in claim construction, as respondents assert. Resp. Br. 21 (citing *Markman*, 517 U.S. at 388-90). If all aspects of claim construction were purely legal, there would have been no colorable claim to a jury determination. What made the judge/jury question complex was that claim construction *does* include facts—the "evidentiary underpinnings" to which the Court referred, 517 U.S. at 390. That is why the Court called it a "mongrel practice." *Id.* at 378. The Court ultimately concluded that the task contained more elements better suited to a court than a jury; either a judge or a jury could competently evaluate testimony, and the judge was far better positioned to "evaluate the testimony in relation to the overall structure of the patent." *Id.* at 390. But the Court did not decree that the "mongrel practice" would from that day on be purebred.

To the contrary, the Court explicitly recognized "that credibility judgments have to be made about the experts who testify in patent cases." 517 U.S. at 389. Sometimes factfinders might even "choose between experts" based on credibility. *Id.* The Court did not anticipate "many cases like that," another reason why claim construction goes to the judge and not the jury. *Id.* But the Court did not signal that there would henceforth be *no* "cases like that"—that the deeply rooted tradition of trial-court factfinding

would be replaced with *de novo* review by the Federal Circuit *even of credibility determinations.*

Rather, *Markman* left them to be reviewed on appeal as district-court credibility judgments are in every other context. Indeed, given respondents' repeated references (at 2, 3, 43, 44, 45) to the notion that experts are paid and therefore less than credible, it is surprising that respondents do not acknowledge district courts' expertise at making *exactly* that sort of credibility determination, subject to clear-error review.[1]

2. No Pre-*Markman* Decision Even Considers The Standard Of Review.

As for the pre-*Markman* decisions respondents cite (at 31-32), nearly all of which predate Rule 52, none even considers the standard of review, much less endorses *de novo* review of facts. U.S. Br. 20 n.2. That is why Judge Hand was able to write in 1950—after all of respondents' cases—that "how the art understood [a claim] term ... was plainly a question of fact; and unless the finding was 'clearly erroneous,' we are to take this definition as controlling." *Harries*, 183 F.2d at 164.

Indeed, in *none* of these cases did the Court indicate its disagreement with the trial court's assessment of the evidence supporting its claim-construction decision, let alone reverse any subsidiary determinations based on the evidence. In one example, the Court reversed the trial court's con-

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[1] *See, e.g., Intertrust Techs. Corp. v. Microsoft Corp.*, 275 F. Supp. 2d 1031, 1044 (N.D. Cal. 2003) (finding "not credible" an opinion "created for this litigation").

struction of a disputed claim not because it disagreed with the court's assessment of the evidence, but because of a legal error: the court's claim construction was not "in conformity with the self-imposed limitations ... contained in the claims." *Coupe v. Royer*, 155 U.S. 565, 576-77 (1895). In others, the Court concluded that the meaning of the disputed claim terms was readily determinable solely by reference to the claim language and specification. *Loom Co.*, 105 U.S. at 590 ("[T]he meaning of this claim is quite obvious. If any explanation of it is needed, it can be readily derived from the body of the specification."); *Tilghman v. Proctor*, 102 U.S. 707, 729-30 (1880) ("The true construction of this claim is to be sought by comparing it ... with the context of the specification ...."). Looking at the record is not *de novo* review, and relying on testimony that "was in no wise impeached or contradicted," *United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 233 (1942), is hardly the same as second-guessing the trial court when the evidence *is* contradicted.

3. The Facts Underlying Claim Construction Are Adjudicative Facts That Require Evidence.

After their initial stab at suggesting that *Markman* resolved this issue, respondents retreat to the notion that the type of facts necessary to construe a patent are invariably *legislative* facts—which require no testimony at all and which appellate courts can weigh, re-weigh, ignore, or find for themselves. The Federal Circuit has never itself advanced that novel justification. And it is fundamentally flawed. Scientific facts that inform the interpretation of a particular document, and thus bear on a dispute between

two parties, are classic *adjudicative* facts, which must be established "through the introduction of evidence," Fed. R. Evid. 201 advisory committee's note (1972), and reviewed under Rule 52(a). Legislative (or "non-evidence") facts, by contrast, are used "in the formulation of a legal principle or ruling by a judge or court or in the enactment of a legislative body." *Id.* The construction of a single patent claim is not a legislative endeavor, and the scientific facts that bear on claim construction are adjudicative facts reviewed under Rule 52(a)(6).

First, respondents contend (at 26-27) that because the skilled artisan is *hypothetical*, figuring out what she would know and understand must be a legal question. Respondents cite no authority for that proposition, and it is a red herring. The law often assumes away gaps in individuals' knowledge by hypothesizing a fully-informed individual. But what that hypothetical individual would have known or concluded at a particular time is a question of *fact*. *See TSC Indus., Inc. v. Northway, Inc.*, 426 U.S. 438, 450 (1976) (what "inferences a 'reasonable shareholder' would draw from a given set of facts" is "for the trier of fact"); *see also United States v. Kubrick*, 444 U.S. 111, 122-23 (1979) (treating medical standard of care as question of historical fact).

Second, and more fundamentally, the "legislative fact" concept does not encompass the type of historical scientific evidence, drawn from the time of the patent application, that sheds light on the meaning of the particular patent-in-suit. "[J]udges are not scientists," *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 148 (1997) (Breyer, J., concurring), and they are not

equipped to take in and resolve a scientific dispute on the basis of their own experience.

When a text has been written by and for specialists, establishing the usage among those specialists presents a predicate "question of fact"—and not legislative fact. *Great N. Ry. Co. v. Merchants Elevator Co.*, 259 U.S. 285, 293 (1922); Pet. Br. 32-33. Respondents try to distinguish those holdings away by pointing out that, in the tariff context, such findings were made by an administrative agency with nationwide jurisdiction. That argument confuses cause and effect: *because* this Court held that the specialized meaning was a question of fact, that question was one for the factfinder (the agency). And the Court noted that the specialized meaning of a term is likewise a factual question under basic contract law, *see id.* at 292 & n.1 (citing cases), which of course owes nothing to the idea of a single nationwide factfinder.

That rule does not change when the predicate facts are scientific facts. *See, e.g.*, *Maine v. Taylor*, 477 U.S. 131, 146 (1986) (even in constitutional case, mandating deferential review of question whether "scientifically accepted techniques" existed). Respondents suggest (at 28) that *Brown v. Piper*, 91 U.S. 37 (1875), lets courts garner scientific background knowledge from wherever they wish, but they overlook what this Court said: before taking notice of a fact not in evidence, "[c]are must be taken that the requisite notoriety exists," and "[e]very reasonable doubt upon the subject should be resolved promptly in the negative." *Id.* at 43; *see* Fed. R. Evid. 201(b); Pet. Br. 24. If federal appellate courts truly could consider whatever contested "scientific"

facts they wished, unconstrained by evidence, that would thoroughly transform litigation in a host of areas—from products liability to environmental law. But no other federal appellate court has asserted such power, and with good reason.

The *historical* nature of claim construction provides even clearer confirmation that the necessary scientific grounding consists of adjudicative facts that may be unique to each patent dispute. Patents are interpreted by referring not to present-day scientific understanding, but to what a skilled artisan would have known when the patent was filed. *Nautilus*, 134 S. Ct. at 2128.[2] That is a fact-sensitive matter, Pet. Br. 31; *cf. TSC Indus.*, 426 U.S. at 450, that requires inquiry into the state of scientific knowledge at a specific time, to resolve a single debate over a single patent. That is adjudicative fact-finding, and it must follow the rules of evidence—except for facts "that are so firmly established as to have attained the status of scientific law," which "properly are subject to judicial notice." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 592 n.11 (1993). The contested scientific facts in this case plainly do not meet that standard.

4. There Is No Policy Justification For Ignoring Rule 52.

Respondents' final submission, echoed by their *amici*, is that review *should* be *de novo*, essentially notwithstanding Rule 52(a). Once the Court con-

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[2] *E.g., EON Corp. IP Holdings, LLC v. FLO TV Inc.*, 2014 WL 906182, at *6 n.9 (D. Del. Mar. 4, 2014) (requiring expert evidence "to resolve the dispute about the capabilities of a computer in 1991").

cludes that "fact[s]," under the Rule, include scientific facts necessary to understand the technology and terminology in a patent, these policy arguments are beside the point.[3] But they are also incorrect on their own terms, because they ignore the current rule's deleterious effect on accuracy, predictability, cost, and settlement, and the sole value they claim this rule serves—"uniformity"—is overstated.

First, the current no-deference rule heightens uncertainty and discourages settlement by holding out the possibility of an appellate do-over. ABA Br. 18-20; AIPLA Br. 15-16; Menell Br. 17. Respondents (at 42) invoke the unresponsive point that *earlier* claim construction promotes settlement. But claim construction can be done early even if it involves factual submissions. Respondents are looking at the wrong variable: what impedes settlement after claim construction is that *de novo* review reduces the district court's claim construction to just an opening bid. *See Lighting Ballast*, 744 F.3d at 1313 (O'Malley, J., dis-

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[3] The closest thing to a *legal* argument in these passages of respondents' brief is the assertion (at 41) that Congress has endorsed the current no-deference regime through sheer inaction. But respondents' citations show only that Congress believed that the Federal Circuit reverses too many claim constructions—hardly a ringing endorsement of *de novo* review. *See* S. Rep. No. 110-259, at 27-28 (2007). Furthermore, this Court has regularly noted the "danger of placing undue reliance" on the notion that congressional "failure to act" equals "congressional 'ratification.'" *Patterson v. McLean Credit Union*, 491 U.S. 164, 175 n.1 (1989). Just because Congress has not acted to reverse *a nonstatutory Federal Circuit precedent from 1995*, one that this Court has never endorsed, does not mean that Congress agrees with it—quite unlike Congress's acquiescence in the venerable doctrine of equivalents laid down *by this Court*, *see* Resp. Br. 41.

senting). What would promote settlement would be to make district-court constructions *meaningful*.

Second, and relatedly, appellate second-guessing of the facts leads to inaccurate, unpredictable decisionmaking. Pet. Br. 20-21, 24. Judge O'Malley, a former district judge now on the Federal Circuit, speaks from experience when she says that "[the Federal Circuit] is given free rein to interpret claim terms, but lacks the resources to do it right." *Lighting Ballast*, 744 F.3d at 1313 (dissenting opinion). The Federal Circuit may have technical advisers on staff and a few judges with training in *a* scientific field, but it does not and cannot call on true skilled artisans from every conceivable art. A college degree in the art usually will not suffice, and a doctorate may not either. *Cf.* J.A. 914a-15a (ordinary skill in the art in this case required a Ph.D. *and* extensive experience in polymer synthesis). And even if the Federal Circuit could obtain direct access to scientists skilled in every conceivable art, it cannot subject their input to the extended, meaningful adversarial testing that the district-court setting allows. Treating district courts' findings with the respect Rule 52(a) requires will encourage district courts to conduct just such testing, *and* to explain their conclusions in a way that the Federal Circuit can review (deferentially) and fellow district courts can follow (because of their persuasive value). Menell Br. 17-18; Pet. Br. 48.

Third, amici again miss the mark when they suggest that expert evidence in claim construction is the problem. Google Br. 11, 19. This Court has entertained such evidence for over a century, the Federal Circuit accepts it, and trial courts welcome it. The

question, rather, is whether findings of scientific fact in patent cases should be treated on appeal like all other findings, or ignored at the Federal Circuit's pleasure.

Fourth, respondents fundamentally misconceive the Federal Circuit's role in promoting uniformity. Having a single patent appeals court put a stop to forum-shopping based on different *legal rules* in different circuits, such as different standards for holding a patent obvious. Pet. Br. 45-46. Respondents identify no comparable history suggesting the Federal Circuit was meant to drum facts out of claim construction in the name of intra-patent uniformity.[4]

The creation of a single patent appeals court did not redefine "law" and "fact," or make an exception to Rule 52(a). Congress consciously did not create a specialized *trial* court; it left patent factfinding to be done by district judges as they have always done. If facts underlying claim construction were governed by Rule 52(a) before the Federal Circuit was created, *see Harries*, 183 F.2d at 164, they are still governed by Rule 52(a).

Federal courts certainly can work toward uniformity while respecting Rule 52(a), using a number of different tools. Issue preclusion is one. Pet. Br. 47. Another is the multidistrict-litigation statute, 28 U.S.C. § 1407, which permits coordination of just such pretrial matters as claim construction.[5] Per-

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[4] Forum-shopping based on how circuits view the law is considerably easier than forum-shopping based on how individual judges *might* find facts relevant to one patent.

[5] Intel notes (at 15) that a recent amendment to the Patent Act restricts "consolidat[ion] for trial." 35 U.S.C. § 299(b). But nothing restricts the multidistrict-litigation panel from order-

suasion is a third: district courts can follow each other's reasoned opinions—opinions which they will have greater incentive to write if their factual findings are respected on appeal. *See, e.g.*, Peter S. Menell, et al., *Patent Case Management Guide* § 5.3.2.5 (Fed. Judicial Ctr. 2009) (citing cases). And the backstop is clear-error review.

In the limited circumstances where claim construction entails factual questions *and* these tools do not lead to consistent answers, patent law, like every other area of law, simply tolerates a degree of variability. Infringement is a factual question. So is the "doctrine of equivalents." So are various patent-invalidity doctrines. Thus, because proof may vary from one action to another, identical devices may be found to infringe the same patent in one case but not in the next. Or the same patent may be found "not invalid" today, invalid tomorrow. Pet. Br. 46-47. That is the consequence of according each new defendant one fair "chance to present [its] evidence and arguments on the [factual] claim." *Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found.*, 402 U.S. 313, 329 (1971). Facts cannot be squeezed completely out of claim construction in the name of "predictability."

Ultimately, absolute Procrustean uniformity is not desirable, especially not at the expense of accuracy. And as the Federal Circuit's decision here illustrates, appellate courts unconstrained by the record are simply more likely to make scientific mistakes.

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ing *pretrial* coordination. *In re Bear Creek Techs., Inc. ('722) Patent Litig.*, 858 F. Supp. 2d 1375, 1378-79 (J.P.M.L. 2012).

II. The Federal Circuit's Decision Rests On Its Failure To Defer.

This Court could answer the question presented simply by disapproving the Federal Circuit's rule that there *are* no factual issues in claim construction, and remanding to apply the ordinary fact/law distinction set out in Rule 52(a). *See* Pet. i. But if this Court chooses to use this case to illustrate how that fact/law distinction applies in the patent context, the outcome is clear. The Federal Circuit considered three aspects of the patent: the use of SEC; Figure 1; and the prosecution history. Each is the subject of an express factual finding by the district court. And in each respect the Federal Circuit's decision cannot be reconciled with that finding. This Court therefore should reverse that decision, either outright or with instructions to construe the patent in accordance with the district court's findings, which respondents have never challenged.

A. Factfinding Appropriately Considers Both Technology And Terminology

District courts are engaged in factfinding when they seek to understand the science or technology discussed in the patent, *cf. Graham*, 383 U.S. at 17, or determine the accepted meaning of particular scientific or technical terminology at the relevant time. Courts turn to the *legal* enterprise of claim construction when they apply that factfinding to the claim language and determine the extent to which the historical facts inform the meaning of the claims. *Cf. Great Northern*, 259 U.S. at 292 ("Where ... the peculiar meaning of words ... is proved by evidence, the

function of construction is necessarily preceded by the determination of the matter of fact.").

Some cases will require no factfinding, because the disputed term either is an ordinary word with no technical meaning, or is defined in the patent itself. In other cases, the court will find as a fact the commonly accepted meaning of a term among skilled artisans at the relevant time, but then decline to apply that commonly accepted meaning as a matter of law. For instance, courts presume that a patent claim should be construed, if possible, not to exclude the embodiments of the invention recited in the specification.[6] Applying that principle to reject the commonly accepted meaning of a term involves a legal conclusion. *See* U.S. Br. 22.

Respondents contend (at 43-44) that fact evidence can pertain only to what is true in the world generally, and that relating scientific facts to the patent is exclusively the job of the court. But some testimony that respondents (and the government to some degree, *see* U.S. Br. 22, 31) identify as document interpretation is really just an expert's attempt to select the scientific facts that are *relevant* to the task at hand. A scientific term may have two accepted meanings in the field—*e.g.*, one associated with hardware and one with software. An expert would be addressing matters of *fact* if she testifies about both meanings. If the expert looks at the patent, sees that it involves software, not hardware, and testifies about the definition relevant to software, respondents would protest that her testimony is no

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[6] *See, e.g., Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1580-81 (Fed. Cir. 1996) (applying this rule to reject the commonly accepted meaning).

longer "separate and apart" from the patent. But her testimony does not become any less factual just because she addresses the definition that is relevant in context.

The test, therefore, is not whether the expert refers to the patent or instead answers entirely hypothetical questions. Nor does it depend on whether the testimony was *live*, Pet. Br. 22-23, particularly where (as here) respondents forwent the opportunity to submit live testimony at trial after the district court denied their summary-judgment motions.

Rather, what matters is whether the expert opines on, and the district court makes findings on, judgments about the science or technology embodied in the patent, or the scientific or technical terminology used in the patent. Those points are factual, not legal.

b. The government's attempt to draw a line between two key issues—the import of Figure 1 to a skilled artisan, and the import of the reference to SEC to a skilled artisan—is fundamentally unpersuasive. Even *amici* recognize that a rule treating one of those issues as factual and the other as legal cannot be correct. Intel Br. 27-28.

The district court properly made *factual* findings on both subjects, which speak directly to the understanding of scientific technique and terminology necessary to understand the patent correctly. Dr. Grant did not impermissibly construe the claim in explaining what Figure 1 *of the patent* would and would not convey to a skilled artisan, because his testimony related to the common scientific understanding of that type of graph. Nor did he impermissibly construe the

claim in explaining what a reference to SEC would convey to a skilled artisan, because his testimony related to the common scientific understanding of how average molecular weight would most likely be measured using SEC.[7]

B. The Federal Circuit Rejected The "Presumed Meaning" Derived From The Reference To SEC.

The district court found that, when certain predicate facts are present, "the *presumed meaning* of [average molecular weight]" to a skilled artisan would be peak average. Pet. App. 43a (emphasis added); *see id.* at 44a. Those predicate facts are (1) the use of SEC to find average molecular weight, and (2) the absence of any further calculations. *See id.* at 43a, 125a; J.A. 138a. No calculations are needed to derive peak average, and none appear in the patent.

That factual finding speaks to both scientific technique and terminology: a scientist's knowledge of technique affects the words she would use to describe the technique's output. And that finding, standing alone, is enough to compel reversal: the panel gave no weight to the "presumed meaning" found by the district court. Instead, the panel treated all three possible measurements of average molecular weight as equally likely, because weight average and number average *can* be obtained from the chromatogram "after some calculations." Pet. App. 10a. That understanding is not compatible with the district court's factual finding.

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[7] The section headings in Dr. Grant's declaration (Resp. Br. 49) are irrelevant. What matters is whether the *district court's findings* are factual in substance, not in labeling.

C. The Federal Circuit Rejected The Correct Scientific Understanding Of Figure 1.

As the government correctly states (at 31-32), the Federal Circuit impermissibly engaged in its own factfinding with respect to Figure 1. The Federal Circuit concluded that Figure 1 refuted Teva's peak-average interpretation, because "the peaks of the curves in Figure 1 do not correspond to" 7.7 kDa. Pet. App. 10a. Respondents insist that that is a legal conclusion, but they cannot escape that the appellate panel was stating a *factual* premise—that if 7.7 kDa was the peak average, then the peaks of Figure 1 *should* correspond to 7.7 kDa—and that the district court had clearly found that that premise is wrong.

That finding was not legal interpretation: it relied on scientific facts, and was grounded in the patent only insofar as the patent discloses what Figure 1 portrays. Pet. App. 141a, 144a. Assessing whether Figure 1 is consistent with Teva's construction requires an understanding of what a chromatogram is, what Figure 1 is, and why they are different. That understanding is factual, even if Figure 1's legal relevance turns on it.

Respondents offer a long digression (at 62-64) on whether Dr. Grant's estimate (J.A. 310a) of weight average was closer to 7.7 kDa than the peak of the Figure 1 curve was.[8] Respondents sought unsuccessfully to impeach Dr. Grant with that argument, *see* 08-cv-7611 ECF No. 141, at 9-10, and they have not

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[8] Notably, *respondents'* expert calculated the weight average in Figure 1 as 12.9 kDa, J.A. 381a, which, if true, would defeat respondents' argument about relative proximity to 7.7 kDa.

challenged the district court's finding as clearly erroneous. The sample's "average molecular weight" (as used in the patent) was 7.7 kDa. Whether the weight average was *close to* 7.7 is irrelevant to whether the peak *of the chromatogram*, and hence the peak average, was *at* 7.7.

The panel thought that because the peak *of Figure 1* does not fall at 7.7 kDa, Figure 1 essentially rules out Teva's interpretation (peak average). *See* Pet. App. 10a. That conclusion flies directly in the face of the District Court's factfinding.

D. The Federal Circuit Rejected The Skilled Artisan's Understanding Of The Mistake In Prosecution History.

Respondents and the court of appeals begin rather than end with the prosecution history. Yet the Federal Circuit has repeatedly cautioned that prosecution history "lacks the clarity of the specification and thus is less useful for claim construction purposes." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc). Mistakes sometimes happen during prosecution, often enough that the Federal Circuit has a number of precedents on how to deal with them.[9] And those precedents start with whether "it [would] have been apparent to a person experienced in this technology that an error was made, or

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[9] That is why, even if a statement to the PTO *can* be read as voluntarily surrendering part of the scope of a claim, the Federal Circuit will not read it that way unless the disavowal was "both clear and unmistakable," not ambiguous. *Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, 508 F.3d 1366, 1371 (Fed. Cir. 2007) (citation omitted).

at least that the information should not be relied upon." *Viskase Corp. v. Am. Nat'l Can Co.*, 261 F.3d 1316, 1322 (Fed. Cir. 2001). Here the district court found that it would. *See* Pet. App. 52a. Indeed, Sandoz's expert *conceded* that it would. J.A. 157a. The Federal Circuit never grappled with that finding.[10]

1. The relevant question is whether a *skilled artisan* would regard two prosecution-history statements as irreconcilable. To accept respondents' argument—that "[t]he skilled artisan 'would have believed that the applicant's disclaiming statements were not a mere mistake,'" Sandoz C.A. Reply Br. 11 (citation omitted)—the Federal Circuit had to substitute its own view for the district court's.

In this Court, respondents act as though the patent became invalid the moment that Teva used the term "weight average," but even on respondents' theory that cannot be right: a statement that "average molecular weight" has a definite meaning cannot make a claim indefinite. Rather, respondents must argue that the claim became indefinite when Teva made a *second* statement to the PTO, a statement that respondents say is irreconcilable with the first.

Whether the statements *are* irreconcilable to a skilled artisan rests on a factual question. A skilled artisan would read the prosecution history as a whole. If an earlier statement is transparently incorrect as a scientific matter, and a later statement

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[10] Respondents suggest (at 52-54) that the Federal Circuit considered this finding, but rejected it as legally irrelevant. The passage respondents quote merely summarizes the parties' *arguments*. *See* Pet. App. 8a. Nowhere does the court actually address its precedent on prosecution-history errors.

is consistent with the best reading of the specification, the skilled artisan would read the later statement as a correction, not as invalidating an entire family of patents. Assessing the premise—that a skilled artisan would recognize that the first statement is an obvious scientific error—is just as factual as understanding chromatography or a graph. The district court found that a skilled artisan would grasp the obvious error and, therefore, see no conflict.

The Federal Circuit made the factual assertion that the "two definitions cannot be reconciled," Pet. App. 9a, ignoring the finding that a skilled artisan would reconcile them by deeming the earlier one an obvious error and the later one a necessary correction. At a minimum, if this Court corrects the standard of review, this issue requires reconsideration with proper deference to the factual record.

2. Respondents assert (at 54) that the "weight average" statement has legal significance even if it is wrong, because if Teva had not told the PTO the correct measure was "weight average," "Teva would not have obtained its patent." But Teva obtained the only remaining patent-in-suit, the '808 patent, nearly *four years* before that statement. *See* Pet. App. 137a; J.A. 1322a.

Respondents argued throughout the district-court proceedings that prosecution history of subsequent patents was *irrelevant* even to the *interpretation* of the '808 patent. *See* Pet. App. 52a-53a. Now they take the opposite position: that even if the '808 patent was definite when it issued, subsequent prosecution history can render it *in*definite. No case from this Court or the Federal Circuit supports this

springing-indefiniteness proposition. Subsequent prosecution history is at most an interpretive aid—a tiebreaker, not a game-changer that can overcome other persuasive indicia of meaning. Even if the prosecution history supported respondents' position, the weight it receives is far from clear now that the other patents are out of the case. That question is more appropriate for the Federal Circuit.[11]

* * * *

What did "average molecular weight" mean to an expert in polypeptide synthesis in 1994? No other court of appeals would regard that question as a legal one, especially if the testifying experts disagreed over it. In every other circuit, the district court's resolution of the expert dispute would get the full measure of appellate deference. In the Federal Circuit, it gets none.

Nothing about patent litigation justifies that departure. To the contrary, the bedrock reasons for deference apply fully in patent cases: appellate fact-finding not only "multipl[ies] appeals by encouraging appellate retrial" of the facts, it "undermine[s] the legitimacy of the district courts in the eyes of litigants." Fed. R. Civ. P. 52 advisory committee's note (1985). This Court should restore district courts and the Federal Circuit to their proper roles.

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[11] Respondents' claim (Br. 65) that there is an urgent need for this Court to resolve claim construction without remanding is without merit. The Federal Circuit can handle remanded cases swiftly. *See Akamai Techs., Inc. v. Limelight Networks, Inc.*, No. 09-1372, ECF Nos. 297, 303 (Fed. Cir.) (argument about nine weeks after remand). Respondents have not obtained the FDA approvals necessary to launch a product in any event.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

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September 10, 2014

AMICUS CURIAE BRIEF

No. 13-854

In the Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
PETITIONERS

v.

SANDOZ, INC., ET AL.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES
AS AMICUS CURIAE SUPPORTING NEITHER PARTY

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QUESTION PRESENTED

Whether, in reviewing a district court's determination that a patent claim is sufficiently clear to satisfy the definiteness requirement of 35 U.S.C. 112, ¶ 2 (2006), the court of appeals should apply a deferential clear-error standard of review to the district court's resolution of subsidiary questions of fact.

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In the Supreme Court of the United States

No. 13-854

TEVA PHARMACEUTICALS USA, INC., ET AL.,
PETITIONERS

v.

SANDOZ, INC., ET AL.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING NEITHER PARTY

INTEREST OF THE UNITED STATES

This case concerns the appropriate standard for appellate review of a district court's determination that disputed patent claims were sufficiently clear to satisfy the definiteness requirement of 35 U.S.C. 112, ¶ 2 (2006). The United States Patent and Trademark Office (PTO) is responsible for "the granting and issuing of patents," 35 U.S.C. 2(a)(1), as well as for advising the President on issues of patent policy, 35 U.S.C. 2(b)(8). The United States therefore has a substantial interest in the Court's resolution of the question presented.

STATEMENT

1. a. A patent is a legal instrument that grants to the patentee "the right to exclude others" from prac-

ticing the claimed invention "throughout the United States or importing the invention into the United States." 35 U.S.C. 154(a)(1).[1] The patent document includes a specification and drawings. 35 U.S.C. 111(a)(2), 113, 154(a)(4). The specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains * * * to make and use the same." 35 U.S.C. 112, ¶ 1. "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. 112, ¶ 2.

Section 112, ¶ 2 requires that "a patent's claims, viewed in light of the specification and prosecution history," must be sufficiently definite to "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc.* v. *Biosig Instruments, Inc.*, No. 13-369 (June 2, 2014), slip op. 11. An inventor's failure to comply with the definiteness requirement renders the claim in suit invalid. See 35 U.S.C. 282(3).

b. In *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), this Court held that, because a patent is a written legal instrument, "the construction of a patent, including terms of art within its claim[s], is exclusively within the province of the court" rather

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[1] In the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, Congress amended several of the provisions implicated here. The amended versions are inapplicable to this case because the patents were filed before the Act's effective date. See Pet. Br. 5 n.4. This brief's citations to Title 35 of the United States Code refer to the 2006 edition.

than the jury. *Id.* at 372. The Federal Circuit subsequently construed *Markman* as mandating that a district court's construction of disputed patent claims, "including any allegedly fact-based questions" resolved on the basis of expert testimony or other extrinsic evidence, is subject to de novo review by the court of appeals. *Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448, 1456 (1998). The en banc Federal Circuit recently considered whether it should overrule *Cybor*, but the court ultimately "confirm[ed] the *Cybor* standard of *de novo* review of claim construction" on *stare decisis* grounds. *Lighting Ballast Control LLC* v. *Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1276-1277 (2014).

2. a. Petitioners are the owner and exclusive licensees of a family of nine patents related to Copaxone®, a drug used in treating multiple sclerosis. Pet. App. 27a-28a. The patents stem from a single patent application and share a common specification. *Id.* at 27a & n.2. Eight of the patents expired in May 2014. *Id.* at 79a-81a. Only the patent known as the '808 patent remains in force; it will expire in September 2015. *Id.* at 81a.

The active ingredient in Copaxone® is "copolymer-1," a mixture of polypeptide molecules of varying sizes. Pet. App. 28a, 31a. The '808 patent recites a method of manufacturing "[c]opolymer-1 having a molecular weight of about 5 to 9 kilodaltons." *Id.* at 5a (emphasis omitted); see *id.* at 3a n.2.

b. In 2008 and 2009, petitioners filed patent-infringement suits against respondents after respondents sought Food and Drug Administration approval to market a generic version of Copaxone®. Pet. App. 26a-28a; see 35 U.S.C. 271(e). As relevant here, re-

spondents argued that certain claims were indefinite because the claim term "molecular weight" has multiple possible meanings and was not defined in the patents' shared specification. Pet. App. 28a.

The district court rejected that argument and held that the claims were not invalid. Pet. App. 26a-72a. The court first explained that, because a mixture like copolymer-1 contains molecules of varying weights, polymer chemists describe the mixture according to its "average molecular weight." *Id.* at 41a. The court further explained that the term "average molecular weight" has no single ordinary meaning with respect to non-uniform compositions like copolymer-1, but instead may refer to any of several different measures, including: peak average molecular weight (M_p), or the molecular weight of the most abundant polymer molecule in the sample; number average molecular weight (M_n), or the arithmetic mean weight of the molecules in the sample; and weight average molecular weight (M_w), which is a weighted average value. *Ibid.*; see *id.* at 4a-5a. Because each measure of molecular weight typically will yield different values for non-uniform compounds, the choice among those alternative meanings dictates what polymer composition the patent claims encompass.

To determine which meaning the term "molecular weight" should be given in petitioners' patent claims, the district court examined the claims, the specification, the prosecution history, and additional evidence, including declarations filed by the parties' respective expert witnesses. Pet. App. 42a, 44a (citing *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1314-1318 (Fed. Cir. 2005) (en banc), cert. denied, 546 U.S. 1170 (2006)). The court held, largely based on the declaration of peti-

tioners' expert, Dr. Grant, that a person of ordinary skill in the art would understand from the specification that, in the patents at issue, the claim term "molecular weight" means M_p. *Id.* at 43a-44a, 48a-49a.

The district court "credit[ed] and accept[ed]" Dr. Grant's testimony that a skilled artisan would understand the patent to refer to M_p because the specification describes measuring the average molecular weight of a copolymer-1 sample using size exclusion chromatography (SEC). Pet. App. 44a. Dr. Grant explained that M_p can be determined directly from SEC-generated data because the "chromatogram" illustrating those data has curves whose "peaks" correspond to the peak average molecular weight for the sample. *Id.* at 43a. Although SEC-generated data can also be used to determine M_w or M_n, further calculations would be necessary. See *id.* at 48a. Dr. Grant further testified that, because the specification did not describe any additional calculations that would be performed to obtain the molecular weight values, a skilled artisan would understand the term "molecular weight" in the patent claims to "mean[] M_p." *Id.* at 49a; see *id.* at 43a. The court "credit[ed]" that testimony. *Id.* at 44a.

The district court rejected respondents' argument that Dr. Grant's inference from the patents' disclosure of SEC was inconsistent with Figure 1 of the patent. Pet. App. 49a. Although Figure 1 depicted a molecular weight distribution curve whose peak values differed from the molecular weight values recited in the specification, the court "credit[ed] all of Dr. Grant's explanation" that converting data from a chromatogram into Figure 1 "would likely cause the peak on each curve to shift slightly." *Id.* at 45a. The court

therefore concluded that Figure 1 "would not dissuade" a skilled artisan from "concluding that [molecular weight] refers to M_p in the context of the patents-in-suit." *Id.* at 49a.

Finally, the district court rejected respondents' argument that the '808 patent was indefinite because petitioners had "proffered contradictory definitions" of "average molecular weight" in prosecuting applications for two related patents. Pet. App. 50a; see *id.* at 45a-47a, 50a-53a. The PTO initially rejected claims in petitioners' applications for what became the '847 and '539 patents on the ground that the term "average molecular weight" was "meaningless" by itself. *Id.* at 51a. Petitioners overcame the '847 rejection by stating that "[o]ne of ordinary skill in the art could understand that kilodalton units implies a weight average molecular weight." *Ibid.* (brackets in original). But petitioners overcame the '539 rejection by representing that a skilled artisan "would understand that 'average molecular weight' refers to the molecular weight at the peak [M_p] of the molecular weight distribution curve shown in Figure 1." *Id.* at 47a, 51a.

The district court credited the testimony of petitioners' expert that, because the term "kilodalton" can be used in reference to any measure of molecular weight, a person of ordinary skill in the art would not infer that the use of the claim term in petitioners' patents implies an M_w measure. Pet. App. 52a. The court concluded that a person of ordinary skill in the art therefore would instead credit the explanation given by petitioners in the prosecution history of the '539 patent. *Ibid.*

3. The court of appeals reversed in relevant part, concluding that the term "molecular weight" was

indefinite. Pet. App. 1a-25a. Reviewing the issue of indefiniteness de novo, *id.* at 7a, the court explained that the claims' "plain language does not indicate which average molecular weight measure is intended," *id.* at 8a. The court concluded that nothing in the specification or prosecution history resolved that ambiguity. *Id.* at 8a-10a.

Reviewing the prosecution history, the court of appeals concluded that petitioners' contradictory representations to the PTO "render[ed] the ambiguity insoluble." Pet. App. 8a-9a. The court explained that petitioners had overcome identical indefiniteness rejections by providing the PTO with two different definitions of "molecular weight" that "cannot be reconciled." *Id.* at 9a.

The common specification of the patents, the court of appeals continued, did "not resolve the ambiguity." Pet. App. 9a. The court acknowledged Dr. Grant's testimony that a skilled artisan would understand that only M_p "can be read directly from a plot of SEC data." *Id.* at 9a-10a. But because it was undisputed that both M_n and M_w could be obtained from SEC data after further calculations, the court concluded that Dr. Grant's testimony did "not save [the] * * * claims from indefiniteness." *Id.* at 10a. The court also held that Figure 1 of the patent undermined the inference that "average molecular weight" means M_p. *Ibid.* The court emphasized that the peaks of the curves depicted in Figure 1 did not correspond to the values recited in the figure's legend as the relevant "average molecular weight" of the sample. *Ibid.*

SUMMARY OF ARGUMENT

I. A patent's claims establish the scope of the patentee's legal rights to exclude others from practicing

the invention. Because a patent is a written legal instrument, the ultimate interpretation of a patent claim—namely, how a person having ordinary skill in the relevant art at the time of the invention would understand the claim—is a question of law for the court. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 372-373 (1996). Courts in patent cases can often resolve interpretive disputes solely by consulting the patent itself—its claims and specification—and its prosecution history. When the court's claim construction is based on those sources alone, no part of its analysis is properly viewed as factual.

In order to understand the relevant science and the technical terms used in the patent, however, a district court often may need to receive additional evidence, such as expert testimony or scientific articles. When a predicate fact is both disputed and material to the court's ultimate claim construction, the court may be required to make factual findings. The Court accordingly observed in *Markman* that, although it is appropriate to "treat[] interpretive issues as purely legal," 517 U.S. at 391, and therefore to allocate interpretive responsibility to the judge, claim construction is a "mongrel practice" that has "evidentiary underpinnings," *id.* at 378, 390.

The standard under which an appellate court should review a district court's claim construction therefore turns on the nature of the district-court ruling under review. While a court's ultimate interpretation of claim language is a legal question reviewed de novo, an appellate court may set aside the lower court's subsidiary factual findings only if it concludes that they are clearly erroneous. See Fed. R. Civ. P. 52(a)(6). The justification for applying

clear-error review is particularly strong in the patent context, as adjudicating patent-law issues often requires familiarity with scientific and technical evidence. Accordingly, this Court has held in the obviousness context that a district court's factual findings—which include the kinds of technical inquiries that are also relevant to claim construction—are subject to Rule 52(a)(6). See *Dennison Mfg. Co.* v. *Panduit Corp.*, 475 U.S. 809, 810-811 (1986) (per curiam). The materially similar factual findings underlying claim construction should receive the same deference.

Applying Rule 52(a)(6) in the claim-construction context is both administrable and consistent with the need to foster uniform treatment of individual patents across multiple proceedings. Courts can distinguish between factual and legal conclusions by assessing the basis for the trial court's decision and the nature of the error asserted on appeal. Factual findings are those that are based at least in part on evidence outside the patent and its prosecution history, and that concern a matter that is in some sense distinct from the meaning or validity of the patent. A court's determination of what a particular claim term means in light of the patent document as a whole is a legal conclusion. Because the ultimate interpretive question remains one of law, there is no reason to think that deferentially reviewing underlying factual findings will lead to disuniformity.

II. These principles of claim construction apply with full force to respondents' contention that petitioners' patent claims using the term "molecular weight" are indefinite. Although the district court's ultimate determination that the claims were not indefinite (and therefore not invalid) was a legal ruling,

that determination was premised in part on findings that are properly characterized as factual.

The Federal Circuit reversed the district court's indefiniteness ruling after engaging in de novo review. Although de novo review was appropriate with respect to the district court's ultimate determination that the challenged claims were not indefinite, the court of appeals was required to accept the district court's factual findings unless it concluded that they were clearly erroneous. The Federal Circuit's indefiniteness analysis was in the main consistent with that requirement. In one respect, however, the court of appeals departed without justification from the district court's factual findings. Although it appears unlikely that this error affected the court of appeals' ultimate holding, this Court should vacate the judgment below and remand the case to allow the Federal Circuit to apply the correct standard of review in the first instance.

ARGUMENT

I. A DISTRICT COURT'S FACTUAL FINDINGS IN CONSTRUING A PATENT CLAIM, AND IN RESOLVING ISSUES OF DEFINITENESS, ARE ENTITLED TO DEFERENCE ON APPEAL

A patent is a legal instrument that grants to the patentee, for a limited term, the right to exclude others in the United States from practicing the claimed invention. *Markman*, 517 U.S. at 373. As with any other legal instrument, the ultimate meaning of a patent claim is a question of law. See *id.* at 372. But the proper construction of a patent claim can sometimes require consideration of evidence outside the patent and its prosecution history, such as expert testimony concerning relevant scientific or technical

principles or the accepted meaning of a specialized term in a particular industry at a particular time. When a district court examines such evidence and resolves disputed questions of fact in order to construe a patent claim, those factual findings "must not be set aside unless clearly erroneous." Fed. R. Civ. P. 52(a)(6).

The same principles apply where, as here, the defendant in an infringement suit argues that a patent claim is invalid because it does not satisfy the definiteness requirement of 35 U.S.C. 112, ¶ 2. The district court's ultimate determination that the claim is or is not indefinite is reviewed de novo on appeal. In conducting that review, however, the court of appeals must accept any subsidiary factual findings made by the district court unless it concludes that those findings are clearly erroneous.

A. The Proper Construction Of A Patent Claim Is An Issue Of Law, But Claim Construction May Involve The Resolution Of Subsidiary Factual Questions

1. Because a patent is a written legal instrument, its construction is ultimately a question of law

a. A patent is an integrated written legal instrument that defines the scope of the patentee's exclusive right to exclude others from practicing the claimed invention. *Markman*, 517 U.S. at 373. The ultimate construction of a patent claim—that is, the determination of the boundaries of the patentee's legal rights—is a question of law. See *id.* at 372; *Bates* v. *Coe*, 98 U.S. (8 Otto) 31, 38 (1878) ("the claims of the patent, like other provisions in writing, must be reasonably construed," and the court must arrive at the "true legal construction"); *Winans* v. *The N.Y. & Erie R.R.*,

62 U.S. (21 How.) 88, 100-101 (1858). That principle is an application of the general rule that the proper interpretation of written instruments that set forth parties' legal rights, such as contracts or deeds, is a question of law. See *State-Planters Bank & Trust Co.* v. *Parker*, 283 U.S. 332, 336 (1931) ("construction of a clause of a deed of trust" is a question of law); *Philippine Sugar Estates Dev. Co.* v. *Government of the Philippine Islands*, 247 U.S. 385, 389 (1918) ("construction of a contract presents a question of law"). And because a patent is a technical document addressed to artisans skilled in the field of the invention, rather than to the "public generally," the ultimate legal question for the district court is how a person having ordinary skill in the relevant art at the time of the invention would understand the claims. *Carnegie Steel Co.* v. *Cambria Iron Co.*, 185 U.S. 403, 430, 437 (1902); see *Nautilus, Inc.* v. *Biosig Instruments, Inc.*, No. 13-369 (June 2, 2014), slip op. 8-9.

b. In conducting that inquiry, a court must construe a patent's claims "in light of the patent's specification and prosecution history." *Nautilus*, slip op. 8. Those sources constitute the publicly available record that a skilled practitioner would consult in order to ascertain the scope of the invention. See *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1313-1314, 1317 (Fed. Cir. 2005) (en banc), cert. denied, 546 U.S. 1170 (2006). Courts in patent cases can often resolve interpretive disputes solely by consulting those sources as well as the claims themselves. When the court's claim construction is based on those sources alone, no aspect of the court's analysis is properly viewed as factual.

The specification describes the invention in more detail than do the claims, and it may resolve the prop-

er scope of a disputed claim term by defining a term or disavowing its ordinary meaning. See *Phillips*, 415 F.3d at 1316-1317; *Merrill* v. *Yeomans*, 94 U.S. (4 Otto) 568, 571-572 (1876) (using specification to resolve an ambiguity in the claim). When a court construes claim terms in light of the specification, it engages in the purely legal inquiry of interpreting claim terms in light of the patent document as a whole. See *Seymour* v. *Osborne*, 78 U.S. (11 Wall.) 516, 545-546 (1870) (interpretation of claims in light of specification is "purely a question of construction" for the court); see also *Markman*, 517 U.S. at 388-390 (courts, not juries, traditionally construe legal documents by applying the "standard construction rule" that term must be defined "in a way that comports with the instrument as a whole").

The prosecution history likewise may resolve interpretive questions because a patent applicant's representations to the PTO about the scope of the invention are generally binding in subsequent litigation. See, *e.g.*, *Graham* v. *John Deere Co.*, 383 U.S. 1, 33 (1966). When an applicant narrows her claim or disclaims particular subject matter in response to an examiner's rejection of the claim, the claim should no longer be construed to cover that subject matter. *Biogen Idec, Inc.* v. *GlaxoSmithKline LLC*, 713 F.3d 1090, 1094-1095 (Fed. Cir. 2013). In construing the claims in light of the prosecution history, a court conducts a legal analysis of the extent to which a patentee's representations to the PTO should constrain the exclusive rights conferred on the patentee. See *id.* at 1095; see also *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 733-737 (2002).

2. Courts in patent cases sometimes must resolve subsidiary factual issues in order to construe a claim

a. Because patent claims are construed from the perspective of a skilled artisan at the time of the invention, a district court may need to receive additional evidence, such as expert testimony or scientific articles, in order to understand the relevant science and the technical terms used in the patent claims, specification, and prosecution history. See *Seymour*, 78 U.S. at 546 (a patent may be "so interspersed with technical terms and terms of art that the testimony of scientific witnesses is indispensable to a correct understanding of its meaning"); see also *Markman*, 517 U.S. at 389-390; *Phillips*, 415 F.3d at 1317-1318. Often the background science is essentially uncontested, and the court may base its legal conclusions on agreed-upon scientific principles. But when a predicate fact is both contested and material to the court's ultimate claim construction, a district court may be required to "choose between experts," *Markman*, 517 U.S. at 389, and make appropriate factual findings.

For instance, a district court might need to resolve factual disputes about the accepted meaning in the relevant industry of a term found in a claim, or about the type of data that can be gleaned from a scientific experiment. In the context of obviousness under 35 U.S.C. 103, the Court has described similar issues as "basic factual inquiries." *Graham*, 383 U.S. at 17 (factual questions include "the scope and content of the prior art," "differences between the prior art and the claims at issue," and "the level of ordinary skill in the pertinent art"). The Court has thus recognized that, although "the ultimate question of patent validity"—whether the invention's advancement over the

prior art would not have been obvious to a skilled artisan—"is one of law," that legal question must be answered against the "background" of subsidiary factual findings concerning the understanding of persons skilled in the art and the state of the prior art at a particular point in time. *Ibid.* Those predicate issues are no less factual when they arise in the context of a claim-construction dispute.

b. Although factual findings may "underpin[]" a district court's interpretation of a patent claim, *Markman*, 517 U.S. at 390, they do not themselves determine the proper construction of the claim. It remains for the court to determine the significance of any factual findings in the context of the patent as a whole. *Id.* at 389. For instance, a court may find as a matter of fact that a disputed claim term had a certain meaning to a skilled artisan at the time of the invention. But the court must then undertake a legal analysis to determine whether a skilled artisan would ascribe the same meaning to the term in the specific context of the patent claim at issue. See *Corning* v. *Burden*, 56 U.S. (15 How.) 252, 270 (1853) ("Experts may be examined as to the meaning of terms of art * * * but not as to the construction of written instruments."); *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1582-1583 (Fed. Cir. 1996) (patentee may serve as his own lexicographer). The court's ultimate construction thus remains a question of law. See *Markman*, 517 U.S. at 389-390.

In that respect, claim construction resembles the interpretation of contracts and other written instruments. "When the words of a written instrument are used in their ordinary meaning, their construction presents a question solely of law," but when "technical

words or phrases not commonly understood are employed," "extrinsic evidence may be necessary to establish a usage of trade" or "peculiar meaning." *Great N. Ry. Co.* v. *Merchants Elevator Co.*, 259 U.S. 285, 291-292 (1922) (construing a railroad tariff). In those cases where "the peculiar meaning of words, or the existence of a usage, is proved by evidence, the function of construction is necessarily preceded by the determination of the matter of fact." *Id.* at 292; see *Cox* v. *Hart*, 145 U.S. 376, 387-388 (1892) (deed); *West* v. *Smith*, 101 U.S. (11 Otto) 263, 270 (1879) (contract); *FDIC* v. *First State Bank of Abilene*, 779 F.2d 242, 244 (5th Cir. 1985) (contract).

3. *This Court did not hold in* Markman *that claim construction is a pure question of law*

The Federal Circuit has described this Court's decision in *Markman* as holding that "the totality of claim construction is a legal question to be decided by the judge." *Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448, 1455 (1998); see *Lighting Ballast Control LLC* v. *Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1276-1277 (2014) (en banc). That analysis reflects a misunderstanding of *Markman*. That decision did not hold that claim construction lacks any subsidiary factual components; it merely allocated the task of construing patent claims to the court rather than to a jury.

The Court in *Markman* addressed the question whether the Seventh Amendment's jury-trial guarantee required that juries determine the meaning of "any disputed term of art about which expert testimony is offered," or whether claim construction is "a matter of law reserved entirely for the court." 517 U.S. at 372. The Court concluded that, in light of the relative skills of judges and juries, it is appropriate to

"treat[] interpretive issues as purely legal" and therefore to allocate interpretive responsibility to the judge. *Id.* at 391. The Court's analysis was premised, however, on the recognition that claim construction is not a purely legal inquiry.

The Court thus observed that, although it had sometimes characterized the Seventh Amendment's application as turning on whether the disputed issue was one of fact or law, the Seventh Amendment issue in *Markman* itself could not be resolved on that basis because "construing a term of art following receipt of evidence" is a "mongrel practice." 517 U.S. at 378. After concluding that "history and precedent" provided "no clear answer[]" to the judge/jury allocation question, *id.* at 388, the Court explained that, "when an issue 'falls somewhere between a pristine legal standard and a simple historical fact,'" decisionmaking responsibility has been allocated to the actor who is "better suited" to decide the question, *ibid.* (quoting *Miller* v. *Fenton*, 474 U.S. 104, 114 (1985)). The Court acknowledged that claim construction has "evidentiary underpinnings," *id.* at 390, and that "credibility judgments have to be made about the experts who testify in patent cases," *id.* at 389. The Court concluded, however, that judges were more capable than juries of "evaluat[ing] the testimony in relation to the overall structure of the patent." *Id.* at 390. Accordingly, the Court held that "the construction of a patent, including terms of art within its claim, is exclusively within the province of the court." *Id.* at 372.

Markman thus indicates that the ultimate choice between competing interpretations of a patent claim is a question of law. 517 U.S. at 389-390. But the decision does not suggest that claim construction lacks

any factual component. To the contrary, the Court recognized that factual findings based on extrinsic evidence will sometimes be essential. If the Court had conceived of claim construction as a purely legal inquiry, it would have been unnecessary to examine the relative competence of judges and juries to determine how interpretive responsibility should be allocated. See *id.* at 388.

The Court's analysis in *Markman* focused on cases in which the parties espouse different interpretations of a particular claim term (in *Markman*, the term "inventory," see 517 U.S. at 375), and the district court is asked to choose between them. In this case, by contrast, respondents do not argue that the district court should have adopted a different construction of the claim term "molecular weight." Rather, respondents contend that the patent claims using that term were invalid because, even after consideration of all the relevant evidence, *no* particular construction of that term emerged with sufficient clarity to satisfy the definiteness requirement of 35 U.S.C. 112, ¶ 2. The principles set forth above, however, apply with full force to the resolution of respondents' definiteness challenge. Although the district court's ultimate determination that the claims were not indefinite (and therefore not invalid) was a legal ruling, that determination was premised in part on findings that are properly characterized as factual.

B. Rule 52(a)(6) Requires Deference To A District Court's Subsidiary Factual Findings In Claim Construction

The standard of appellate review of a district court's claim construction depends in part on the range of materials the district court consults. When

the court's construction rests entirely on its assessment of the patent itself and its prosecution history, the court has engaged in a purely legal analysis, see pp. 12-13, *supra*, to which the appellate court owes no deference. But when a district court considers additional evidence and resolves a disputed issue of fact, the court of appeals may set aside that finding only if it concludes that the finding is clearly erroneous.

Rule 52(a)(6) of the Federal Rules of Civil Procedure provides that "[f]indings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility." Fed. R. Civ. P. 52(a)(6). Rule 52(a)(6) "does not make exceptions or purport to exclude certain categories of factual findings from the obligation of a court of appeals to accept a district court's findings unless clearly erroneous." *Pullman-Standard* v. *Swint*, 456 U.S. 273, 287 (1982). The Court has accordingly held that, across all types of civil litigation, "review of factual findings under the clearly-erroneous standard—with its deference to the trier of fact—is the rule, not the exception." *Anderson* v. *City of Bessemer City*, 470 U.S. 564, 575 (1985).

Nothing in the Patent Act suggests that district-court factual findings in patent cases are entitled to less deference than Rule 52(a)(6) requires in other contexts. To the contrary, the Court has recognized that the justification for applying clear-error review is particularly strong in the patent context. *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 609-610 (1950). That is because adjudicating patent-law issues sometimes depends on the "testimony of experts or others versed in the technology" and

requires "familiarity with specific scientific problems and principles not usually contained in the general storehouse of knowledge and experience." *Ibid.*

Accordingly, the Court has held in the obviousness context that a district court's factual findings—which include inquiries that are also relevant to claim construction, see pp. 14-15, *supra*—"ought to be subject to the Rule." *Dennison Mfg. Co.* v. *Panduit Corp.*, 475 U.S. 809, 811 (1986) (per curiam); see *Graver Tank*, 339 U.S. at 609-611 (in applying doctrine of equivalents, reviewing district court's findings concerning scientific issues and the content of the prior art for clear error). There is no reason that factual findings made by a district court in choosing between competing constructions of a disputed claim, or in determining whether the claim is sufficiently clear to satisfy 35 U.S.C. 112, ¶ 2, should be given less deference on appeal than the same findings would receive in a validity challenge based on obviousness.[2]

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[2] Contrary to the Federal Circuit's view, see *Lighting Ballast*, 744 F.3d at 1279-1280, historical practice does not support de novo appellate review of factual findings underlying claim construction. This Court did not directly address the standard of review for claim-construction decisions either before or after Rule 52(a)(6) was promulgated in 1937. And even when it reversed or disagreed with aspects of lower-court interpretations, the Court did not suggest that it did so on the ground that the district court had made erroneous fact-findings about extrinsic evidence. See, *e.g.*, *Universal Oil Prods. Co.* v. *Globe Oil & Ref. Co.*, 322 U.S. 471, 473, 482-483 (1944) (affirming lower courts' claim construction based on patent and prosecution history); *United Carbon Co.* v. *Binney & Smith Co.*, 317 U.S. 228, 233-237 (1942) (reinstating district court's indefiniteness ruling based on specification and undisputed inventor testimony); *Exhibit Supply Co.* v. *Ace Patents Corp.*, 315 U.S. 126, 134-137 (1942) (affirming claim construction but reversing application of doctrine of equivalents); *Schriber-Schroth Co.* v.

C. Applying Rule 52(a)(6) To Factual Findings Underlying Claim Construction Is Administrable And Consistent With The Need For Uniformity

The Federal Circuit has articulated two primary policy rationales for de novo review of factual findings underlying claim construction. See *Lighting Ballast*, 744 F.3d at 1283-1286. Those rationales are inconsistent with Rule 52(a)(6)'s clear command and are unpersuasive on their own terms.

1. a. Applying Rule 52(a)(6) in reviewing district-court claim-construction decisions would not, as the Federal Circuit believed, "diminish workability." *Lighting Ballast*, 744 F.3d at 1283-1284. While discerning the "distinction between questions of fact and questions of law" can be "vexing," *Pullman-Standard*, 456 U.S. at 288, federal courts have extensive experience applying the standard, see *First Options of Chi., Inc.* v. *Kaplan*, 514 U.S. 938, 947-948 (1995); *Albemarle Paper Co.* v. *Moody*, 422 U.S. 405, 424 (1975) (standard is "familiar"). In patent cases as elsewhere, courts can distinguish between factual and legal conclusions by assessing the basis for the trial court's decision and the nature of the error asserted on appeal.

A holding by this Court that Rule 52(a)(6) applies, moreover, may have salutary effects that reduce the

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Cleveland Trust Co., 311 U.S. 211, 220-223 (1940) (reversing construction based on prosecution history); *Smith* v. *Snow*, 294 U.S. 1, 10-16 (1935) (reversing court of appeals' claim interpretation and agreeing with district court after reviewing specification in light of "scientific fact"); *Coupe* v. *Royer*, 155 U.S. 565, 574-577 (1895) (reversing construction based on claim language). The Court thus has had no occasion to address the proper standard of reviewing factual findings underlying claim construction.

difficulty of "disentangling" the factual and legal components of district-court claim-construction decisions. *Lighting Ballast*, 744 F.3d at 1284. Under the Federal Circuit's current practice of independently reviewing all aspects of claim construction, district courts have little reason to clearly distinguish factual findings from legal conclusions. District courts are more likely to "disentangl[e]" fact from law in their own decisions if doing so has some operative effect.

b. In order for a finding in this context to qualify as "factual," two criteria must be satisfied. First, the finding must be based at least in part on evidence outside the patent and its prosecution history. Second, the finding must concern a matter that is in some sense distinct from the meaning or validity of a patent claim. For instance, when a district court based on expert testimony finds that a skilled practitioner would understand a term to have a particular meaning when it is used in the relevant field, the court has made a finding of fact. But if the court then determines that the term bears the same meaning in the claim as it does in the field, the court has rendered a legal conclusion. In many cases the legal ruling about the term's meaning in the claim will entail only a small inferential step from the factual finding about its meaning outside the document. Yet the ultimate claim-construction determination remains one of law because it reflects the court's construction of a legal instrument in light of the document as a whole.

Whether a factual or legal challenge is presented will often be readily discernible from the appellant's arguments on appeal. Taking the example just discussed, if the appellant contends that key language in the specification supports a construction of a claim

term different from the term's usual meaning in the field, and that the district court failed to appreciate the significance of that specification language, the appeal will turn on purely legal questions. But if the appellant argues that the court erred in its assessment of historical industry practice, *e.g.*, by crediting an expert whose testimony was unworthy of belief, its appeal will present a factual challenge subject to Rule 52(a)(6).

The instances in which the Federal Circuit must apply clear-error review in this context should be relatively infrequent. Claim construction ordinarily turns on disputes about the correct legal inferences to be drawn from the patent's language and prosecution history rather than disputes about scientific facts. See *Lighting Ballast*, 744 F.3d at 1285. Clear-error review is appropriate only to the extent that the district court has considered additional evidence and rendered clearly identifiable factual findings. And because expert witnesses may "be examined as to the meaning of terms of art * * * but not as to the construction of written instruments," *Corning*, 56 U.S. at 270, a district court's ultimate construction of a patent claim remains legal even if the court purports to credit an expert witness's testimony that a skilled artisan would understand the claim in a particular way.

c. The Federal Circuit was also incorrect in suggesting that, because applying Rule 52(a)(6) in claim construction is unlikely to alter the outcomes of a substantial number of cases, any benefit would be outweighed by the burden of distinguishing between factual and legal questions. See *Lighting Ballast*, 744 F.3d at 1285-1286. Even apart from the court's over-

estimation of the difficulty involved, the fact that applying Rule 52(a)(6) might not alter the outcome of many cases does not justify ignoring its clear command. See *Salve Regina Coll.* v. *Russell*, 499 U.S. 225, 237-238 (1991). The Rule reflects the recognition that district courts are institutionally better placed than appellate courts to make factual findings, and that on balance, deferential appellate review furthers accuracy and conserves judicial and litigant resources. See *Anderson*, 470 U.S. at 574-575.

2. The Federal Circuit has also expressed concern that applying Rule 52(a)(6) will undermine the "'uniformity in the treatment of a given patent' that [this] Court sought to achieve in *Markman*." *Lighting Ballast*, 744 F.3d at 1286 (quoting *Markman*, 517 U.S. at 390). There is no reason to think that reviewing subsidiary factual findings for clear error would often result in the Federal Circuit's affirming "differing district court rulings" construing a single patent. *Ibid.* The Federal Circuit would continue to review de novo the district court's resolution of the legal questions, including questions as to the inferences that should be drawn from factual findings in light of the patent as a whole, that generally predominate in claim construction.[3] See pp. 15-16, *supra*. The court may also overturn clearly erroneous findings.

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[3] In addition, issue-preclusion principles will "ordinarily foster uniformity" by preventing "evidentiary questions of meaning" from being "wide open in every new court in which a patent might be litigated." *Markman*, 517 U.S. at 391 (citing *Blonder-Tongue Labs., Inc.* v. *University of Ill. Found.*, 402 U.S. 313 (1971)).

II. APPLYING THE CLEAR-ERROR STANDARD IN THIS CASE WOULD LIKELY NOT ALTER THE COURT OF APPEALS' INDEFINITENESS HOLDING, BUT THIS COURT SHOULD REMAND TO PERMIT THE COURT OF APPEALS TO CONSIDER THE QUESTION IN THE FIRST INSTANCE

The district court construed the claim term "molecular weight" in the '808 patent to mean peak average molecular weight. The court further held that, "[b]ecause the term 'average molecular weight' is amenable to construction and not insolubly ambiguous, [respondents'] motion for summary judgment on the basis of indefiniteness is DENIED." Pet. App. 62a (brackets and some internal quotation marks omitted); see *id.* at 47a-62a. The Federal Circuit reversed, holding that the relevant claim was indefinite because a skilled artisan would not be able to determine which definition of "average molecular weight" the '808 patent incorporates.[4] *Id.* at 6a-10a. The court of appeals explicitly engaged in "*de novo* review of the district court's indefiniteness holding." *Id.* at 10a.

The district court's ultimate determination that the challenged claims were not indefinite was subject to

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[4] The court of appeals used the formulations of indefiniteness that this Court recently discountenanced in *Nautilus*. Compare Pet. App. 6a (claim is indefinite if it is "insolubly ambiguous"), with *Nautilus*, slip op. 11-13 (claim is indefinite if it does not "inform those skilled in the art about the scope of the invention with reasonable certainty"). Because the "insolubly ambiguous" standard "tolerate[s] [more] imprecision" than the *Nautilus* standard, *id.* at 12, and the Federal Circuit found that the claim was indefinite even under the more forgiving standard, the court's use of the incorrect formulation in this case did not affect the outcome.

de novo review on appeal. For the reasons set forth above, however, the court of appeals was required to accept the district court's factual findings unless the appellate court concluded that particular findings were clearly erroneous. For the most part, the Federal Circuit's indefiniteness analysis was consistent with that requirement. In one respect, however, the court of appeals departed without justification from the district court's factual findings. Although it appears unlikely that this error affected the court of appeals' ultimate indefiniteness holding, the Court should vacate the judgment below and remand the case to allow the Federal Circuit to apply the correct standard of review in the first instance.

A. The Federal Circuit's Decision Rested Primarily On Its Rejection Of The District Court's Legal Inferences

Petitioners assert (Br. 53-58) that the Federal Circuit effectively overturned without justification three factual findings made by the district court: (1) that petitioners' statement about the meaning of "kilodalton" in prosecuting the '847 patent was scientifically incorrect; (2) that a skilled artisan would infer from the patent's reference to SEC that M_p is the relevant measure of "average molecular weight"; and (3) that any discrepancy between Figure 1's value and M_p was a technical artifact. In evaluating petitioners' claims of error, it is essential to distinguish the district court's factual findings from its subsequent legal inferences. In the government's view, the court of appeals violated Rule 52(a)(6) by relying on Figure 1 in a way that was logically inconsistent with a district-court factual finding. Petitioners' other claims of error lack merit (or at least do not implicate Rule 52(a)(6)), however, because the challenged aspects of

the Federal Circuit's analysis take issue with the legal inferences drawn by the district court rather than with that court's factual findings.

1. The court of appeals did not overturn, or reach a conclusion logically inconsistent with, the district court's factual finding that petitioners' prosecution-history statement about the word "kilodalton" was inaccurate.

a. In the district court, respondents contended that petitioners' inconsistent prosecution-history statements about the meaning of "molecular weight" in related patents demonstrated that a skilled artisan would be unable to discern which measure of "molecular weight" the claims contemplated. Pet. App. 50a-51a. In responding to an initial rejection of the '847 patent application, petitioners told the examiner that "[o]ne of ordinary skill in the art could understand that kilodalton units implies a weight average molecular weight [M_w]." *Id.* at 51a (first set of brackets in original). The district court found (and the parties do not dispute) that this statement was scientifically "incorrect," and that a person skilled in the art would know it was incorrect, because the term "kilodalton" is used in reference to each different measure of molecular weight. *Id.* at 52a. That is a finding of fact concerning scientific principles and understandings as they exist in the field, outside the patent document.

The district court then concluded that, because the '847 prosecution-history statement was scientifically incorrect, a person skilled in the art would disregard the statement entirely, "would not conclude that" the claim term "molecular weight" "implies" M_w, and would instead conclude that the term referred to M_p on the basis of "the '539 patent prosecution state-

ment." Pet. App. 52a (internal quotation marks omitted). Those conclusions are legal, because they concern the relative weight that a skilled artisan *interpreting the patent claims* would accord each prosecution-history statement in light of the fact that one of the statements contained a scientific inaccuracy. The legal nature of that conclusion is not negated by the district court's characterization of its conclusion as a "finding" based on Dr. Grant's assertions about how a skilled artisan would understand the claim term. *Ibid.* The ultimate interpretive significance of representations in the prosecution history is a matter of law for the court to decide—even if, as here, the parties offer their preferred interpretations through the opinion testimony of expert witnesses. *Winans*, 62 U.S. at 100-101; see p. 23, *supra*.

b. The court of appeals, without mentioning the district court's finding about the inaccuracy of the '847 statement, held that petitioners' "prosecution statements directly contradict each other and render" the '808 patent indefinite. Pet. App. 8a-9a. The court emphasized that the "plain language [of the patents] does not indicate which average molecular weight measure is intended." *Id.* at 8a. The court then explained that the "only basis upon which the Examiner could have agreed that the '539 patent claims were not indefinite was that 'molecular weight' means M_p," while the "only basis for the Examiner's withdrawal of the indefiniteness rejection of the '847 patent claims was that the same term means M_w." *Id.* at 9a. The court observed that these alternative explanations of the same term "cannot be reconciled." *Ibid.*

In the court of appeals' view, the salient point for indefiniteness purposes was that the PTO had issued

two patents based on petitioners' irreconcilable representations about what "molecular weight" meant in the claims. It is unclear whether the Federal Circuit overlooked the district court's finding that the '847 prosecution-history statement was erroneous, or whether it simply regarded that fact as ultimately insignificant to the indefiniteness inquiry. In either event, there is no sound reason to conclude that the Federal Circuit rejected, or analyzed the case in a manner logically inconsistent with, the district court's factual finding. In particular, nothing in the Federal Circuit's opinion suggests that the court decided the case on the misunderstanding that the term "kilodalton" actually implies M_w. Petitioners appear to argue (Br. 57-58) that, in light of the district court's finding that one of petitioners' prosecution-history statements was scientifically incorrect, the court of appeals should have attached less weight to the existence of the inconsistent statements. But arguments concerning the significance of particular facts to the overall legal analysis, whatever the merits of those arguments, have nothing to do with Rule 52(a)(6) or with the standard-of-review question on which this Court granted certiorari.

2. The court of appeals next concluded that the patent's reference to SEC did not "resolve the ambiguity" created by the prosecution history. Pet. App. 9a-10a. Contrary to petitioners' contention (Br. 56-57), the court did not overturn or implicitly reject the district court's factual findings concerning SEC.

a. The district court concluded that a skilled artisan would understand the patent's reference to SEC to indicate that "molecular weight" means M_p. Pet. App. 43a-45a. The court first credited Dr. Grant's

testimony, which respondents did not dispute (*id.* at 48a-49a), that "M_p can be read from the chromatogram generated by SEC without any further calculation." *Id.* at 43a (internal quotation marks omitted). The court further found, based on the testimony of both parties' experts, that SEC "can also provide M_w and M_n" if further calculations are performed. *Id.* at 48a. Those determinations are findings of fact about the types of data that can be generated by particular methods of measurement.

Ultimately, the court "credit[ed] Dr. Grant's representation" that, because the specification does not disclose additional calculations, "a person of ordinary skill in the art would understand that [molecular weight] means M_p" in the claims. Pet. App. 48a-49a. That conclusion, though phrased as a credibility finding, is a legal determination of how a skilled artisan would interpret the claim's use of "molecular weight" in light of the specification's reference to SEC. See p. 23, *supra*.

b. The court of appeals acknowledged Dr. Grant's testimony that "only M_p * * * can be read directly from a plot of SEC data." Pet. App. 10a. But the court additionally took note of the undisputed fact that "M_n and M_w can also be obtained from the data generated by the SEC method after some calculations." *Ibid.* The court concluded that "Dr. Grant's testimony does not save [the] claims from indefiniteness." *Ibid.*

That reasoning is not inconsistent with the district court's finding that only M_p can be gleaned from SEC without further calculations. A skilled artisan could accept that SEC generates M_p directly but conclude that, because SEC data can also be used to calculate

M_n and M_w, the specification's reference to SEC does not resolve the ambiguity concerning the claim term "molecular weight." The district court concluded that Dr. Grant's testimony concerning the data that SEC can generate, *combined with* the absence of any reference in the patent to the additional calculations that would be needed to determine M_n or M_w, indicates that "molecular weight" in the claims means M_p. Pet. App. 48a-49a. But determinations concerning the appropriate inferences to be drawn from other portions of the patent itself are legal rather than factual in nature. Even assuming, *arguendo*, that the court of appeals unjustifiably disregarded the absence of any reference within the patents to additional calculations, its error had nothing to do with the standard of review that applies to district-court factual findings.

3. Finally, the court of appeals did engage in impermissible de novo fact-finding with respect to Figure 1 of the patent. Pet. App. 10a.

a. In the district court, respondents argued that Dr. Grant's assertion that the patent referred to M_p was inconsistent with the molecular weight distribution curve depicted in Figure 1 of the patent, the peak values of which do not correspond to the molecular weight values recited in the body of the specification. Pet. App. 49a. The court rejected that argument, "credit[ing] all of Dr. Grant's explanation" that converting data from a chromatogram to a molecular weight distribution curve, such as that shown in Figure 1, "would likely cause the peak on each curve to shift slightly." *Id.* at 44a-45a. That explanation of how a skilled artisan would understand a distribution curve created from chromatogram data is a finding of fact. The court then reached the legal conclusion that

a person skilled in the art, considering Figure 1 in light of the knowledge that the curves would have shifted, "would not [have been] dissuade[d] * * * from concluding that [molecular weight] refers to M_p in the context of the patents-in-suit." *Id.* at 49a.

b. The court of appeals, however, observed that "the peaks of the curves in Figure 1 do not correspond to the values denoted as 'average molecular weight' in the figure's legend," and stated that it was therefore "difficult to conclude that M_p is the intended measure." Pet. App. 10a. The court thus relied on Figure 1 in a way that was logically inconsistent with the district court's factual finding that a skilled artisan would understand that the peaks of a distribution curve would have shifted in the data conversion process. If the court of appeals had accepted that finding, it could not have concluded on the basis of the discrepancy alone that Figure 1 undermined the case for M_p.

B. Although Applying Clear-Error Review Would Likely Not Alter The Court Of Appeals' Holding That The Patent Is Indefinite, Remanding To The Federal Circuit Would Be Consistent With This Court's Ordinary Practice

The court of appeals' disregard of the district court's factual finding concerning Figure 1 likely did not affect its ultimate conclusion that the claim of the '808 patent is indefinite. The court of appeals' indefiniteness holding appeared to rest primarily on its conclusion that petitioners' prosecution-history statements "render[ed] * * * insoluble" the ambiguity created by the patent's failure to define "molecular weight." Pet. App. 8a-9a. The court then held that the specification—its reference to SEC and Figure

1—did "not resolve the ambiguity" created by the prosecution history. *Id.* at 9a.

Even if the court of appeals had accepted the district court's findings about Figure 1, the court would not likely have concluded that the specification shed any light on the meaning of "molecular weight." The court of appeals appears to have viewed Figure 1's failure to illustrate M_p values as an *additional* reason to conclude that the specification's reference to SEC did not resolve the ambiguity concerning the claim term "molecular weight." See Pet. App. 10a ("Furthermore, * * * the peaks of the curves in Figure 1 do not correspond" to M_p.). Even if the court had accepted the district court's finding as not clearly erroneous, then, it is unlikely that this finding alone would have led the Federal Circuit to hold that a skilled artisan would understand with reasonable certainty that the patent claim referred to M_p.

When a court of appeals has applied an incorrect legal standard, however, this Court's "ordinary practice" is to remand so that the court of appeals "can reconsider" its decision "under the proper standard." *Nautilus*, slip op. 14. Although it appears likely that the Federal Circuit will ultimately reaffirm its conclusion that the patent is indefinite, the Court should remand in order to permit the Federal Circuit to consider in the first instance whether deferring to the district court's factual findings affects its ultimate decision.[5]

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[5] Remanding could have the effect of depriving respondents of any practical benefit of a judicial ruling that the claim of the '808 patent is invalid. When the '808 patent expires in September 2015, respondents will be able to market their generic versions of Copaxone® regardless of whether the patent is valid. See Br. in Opp.

CONCLUSION

The judgment of the court of appeals should be vacated and the case remanded for further proceedings.

Respectfully submitted.

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JUNE 2014

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1. It is uncertain whether any remand proceedings could be completed substantially before September 2015.

AMICUS CURIAE BRIEF

No. 13-854

In the
Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. AND YEDA RESEARCH AND DEVELOPMENT CO., LTD.,
Petitioners,

v.

SANDOZ INC., MOMENTA PHARMACEUTICALS, INC., MYLAN PHARMACEUTICALS INC., MYLAN INC. AND NATCO PHARMA LTD.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF THE AMERICAN BAR ASSOCIATION AS *AMICUS CURIAE* SUPPORTING NEITHER PARTY

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QUESTION PRESENTED

Rule 52(a) of the Federal Rules of Civil Procedure provides that in matters tried to a district court, the court's "[f]indings of fact must not be set aside unless clearly erroneous."

The question presented is as follows:

Whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel did in this case), or only for clear error, as Federal Rule of Civil Procedure 52(a) requires.

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STATEMENT OF INTEREST[1]

The American Bar Association ("ABA") respectfully submits this brief in support of neither party. The ABA urges this Court to hold: (i) that the Federal Circuit should review findings of fact made during claim construction under the clearly erroneous standard, pursuant to Federal Rule of Civil Procedure 52(a)(6), and (ii) that any Federal Circuit precedent providing for *de novo* review of factual findings underlying claim construction, including the *en banc* Federal Circuit decisions in *Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) ("*Cybor*"), and *Lighting Ballast Control LLC v. Philips Electronics North America Corp.*, 744 F.3d 1272 (Fed. Cir. 2014) ("*Lighting Ballast*"), should be overruled.

The ABA is the leading national organization of the legal profession, with nearly 400,000 members from all 50 states, the District of Columbia and the U.S. territories. Membership is voluntary and includes attorneys in private practice, government service, corporate law departments and public interest organizations. ABA members comprise judges, legislators, law professors, law students and non-lawyer

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[1] Pursuant to Rule 37.6, *amicus curiae* certifies that no counsel for a party authored this brief in whole or in part and that no person or entity, other than *amicus*, its members or its counsel, has made a monetary contribution to the preparation or submission of this brief. Sup. Ct. R. 37.6. The Mylan and Natco Respondents' blanket consent to the filing of *amicus* briefs is on file with the Clerk of the Court. Letters of consent from Petitioners and the Sandoz and Momenta Respondents accompany this brief.

"associates" in related fields, and represent the full spectrum of public and private litigants.[2]

The ABA Section of Intellectual Property Law ("IPL Section"), which was established in 1894, is now the world's largest organization of intellectual property professionals. The IPL Section has approximately 25,000 members, including attorneys who represent patent owners, accused infringers, individual inventors, large and small corporations and universities and research institutions across a wide range of technologies and industries. The IPL Section works to promote the development and improvement of intellectual property law and takes an active role in addressing proposed legislation, administrative rule changes and international initiatives regarding intellectual property. It also develops and presents resolutions to the ABA House of Delegates for adoption as ABA policy to help foster necessary changes to the law.[3] These policies provide a basis for the preparation of

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[2] Neither this brief nor the decision to file it should be interpreted to reflect the views of any judicial member of the American Bar Association. No inference should be drawn that any member of the Judicial Division Council has participated in the adoption or endorsement of the positions in this brief. This brief was not circulated to any member of the Judicial Division Council prior to filing.

[3] Only the recommendations adopted by a vote of the ABA's House of Delegates (but not their accompanying reports) become ABA policy. The House of Delegates is composed of 560 delegates representing states and territories, state and local bar associations, affiliated organizations, sections and divisions, ABA members and the Attorney General of the United States, among others. *See* ABA, *House of Delegates General Information*, http://www.americanbar.org/groups/leadership/delegates.html (last visited June 19, 2014).

ABA *amicus curiae* briefs, which are filed primarily in this Court and the United States Court of Appeals for the Federal Circuit.[4]

Through their collaborative process, the diverse members of the IPL Section have developed a consensus position on the appropriate standard of appellate review for district court findings of fact during claim construction. This position was presented to the ABA House of Delegates as Resolution #302 and adopted as ABA policy in August 2004.[5] This policy, which has been the basis of several prior ABA *amicus* briefs,[6] supports appellate review of the ultimate claim construction *de novo*, but urges that any underlying findings of fact made in connection with construing a claim term be reviewed under the clearly erroneous standard.

The ABA takes no position on which party should prevail in the present case. However, based on its members' considerable experience with the effects of the Federal Circuit's current *de novo*

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[4] *See* ABA, *Amicus Curiae Briefs*, http://www.americanbar.org/amicus/1998-present.html (last visited June 19, 2014).

[5] Resolution No. 302, without its attendant Report, accompanies this brief.

[6] The ABA has previously filed *amicus* briefs on this subject in support of the petition for *certiorari* filed in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039 (Fed. Cir. 2006), *cert. denied*, 550 U.S. 953 (2007), and in support of neither party in the Federal Circuit *en banc* decisions in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), and *Lighting Ballast Control LLC v. Philips Electronics North America Corp.*, 744 F.3d 1272 (Fed. Cir. 2014).

standard on businesses and individuals across a wide range of technologies and industries, the ABA believes that its insights may be of assistance to this Court.

SUMMARY OF ARGUMENT

The ABA urges this Court to hold that factual findings made in support of a district court's claim construction be reviewed only for clear error, as prescribed by Federal Rule of Civil Procedure 52(a)(6). The ABA also respectfully requests that this Court overrule any contrary Federal Circuit precedent requiring *de novo* review of factual findings made during claim construction, including the *en banc* decisions in *Cybor* and *Lighting Ballast*.

1. The Federal Circuit's *de novo* standard of review for the factual matters underlying claim construction stems from the majorities' holdings in *Cybor* and *Lighting Ballast* that claim construction is a purely legal matter. This Court, however, has previously classified claim construction as a mixed question of fact and law. Moreover, the evaluation of intrinsic and extrinsic evidence by district courts during claim construction necessarily involves the determination of issues of fact. These include determining the level of skill in the art, evaluating the patent specification and prosecution history and assessing the value of any expert testimony. The hybrid nature of claim construction thus demands a hybrid standard of review: a *de novo* assessment of the ultimate claim construction, and clear error review for the factual matters underlying this determination.

2. Neither the *Cybor* nor *Lighting Ballast* majorities have attempted to square *de*

novo review with Federal Rule of Civil Procedure 52(a)(6), which states that "[f]indings of fact must not be set aside unless clearly erroneous." Fed. R. Civ. P 52(a)(6). This Court has noted that Rule 52(a) applies to all factual findings in actions tried before a judge. It has also explained that factual findings underlying other mixed issues of patent law, *e.g.*, obviousness, should be reviewed for clear error pursuant to Rule 52(a)(6). The departure from the "clear error" standard in the claim construction context should thus be corrected.

3. *De novo* appellate review of factual findings ignores the proper role of district courts, which are best positioned to make findings of fact during claim construction. Applying a *de novo* standard of review undermines confidence in trial court *Markman* rulings. It also often results in overruling a district court construction that is based on first-hand access to witnesses and other evidence, in favor of an appellate interpretation of patent claims based solely on the written record. Clear error review pursuant to Rule 52(a) would therefore reestablish the traditional role of the trial court as a finder of fact.

The rule espoused in *Cybor* and *Lighting Ballast* has led to high reversal rates for district court claim construction rulings at the Federal Circuit. The resulting unpredictability regarding appellate outcomes has left the patent community lacking in guidance as to how patent claims should be drafted, interpreted and litigated. In addition, the increased uncertainty that has resulted from *de novo* review has led to longer and more costly lawsuits and has discouraged settlement. By increasing predictability, clear error review of district court factual findings would alleviate these problems.

ARGUMENT

I. Claim Construction Involves Numerous Underlying Findings of Fact

In *Markman v. Westview Instruments, Inc.*, this Court explained that claim construction is a mixed issue, "somewhere between a pristine legal standard and a simple historical fact." *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996). Because claim construction is a "mongrel practice" with "evidentiary underpinnings," this Court has never viewed it as anything but a mixed question of fact and law. *Id.* at 378, 390; *see also Gasperini v. Ctr. for Humanities, Inc.*, 518 U.S. 415, 443 (1996) (Stevens, J., dissenting) (characterizing *Markman* as an opinion about a mixed issue of law and fact).

Notwithstanding this Court's teachings, the Federal Circuit in *Cybor* held that claim construction is "purely [a] legal question." *Cybor*, 138 F.3d at 1456. Nearly two decades later, the *en banc* Federal Circuit reconsidered and reaffirmed this holding. *See Lighting Ballast*, 744 F.3d at 1284 ("Claim construction is a legal statement of the scope of the patent right "). In these cases, the Federal Circuit reasoned that claim construction does not turn on an assessment of extrinsic evidence or witness credibility, but is instead determined by interpretation of "the patent documents" as a matter of law. *Id.* at 1284; *see also Cybor*, 138 F.3d at 1454. Even within the Federal Circuit, however, this basic premise has been a long-standing source of disagreement. *See, e.g., Phillips v. AWH Corp.*, 415 F.3d 1303, 1330-34 (Fed. Cir. 2005) (Mayer, J., dissenting) ("Now more than ever I am convinced of the futility, indeed the absurdity, of this court's persistence in adhering to

the falsehood that claim construction is a matter of law devoid of any factual component We should abandon this unsound course."); *Cybor*, 138 F.3d at 1475 (Rader, J., dissenting) (by claiming district courts do not rely upon extrinsic evidence in making claim construction determinations, the Federal Circuit "'knowingly enters a land of sophistry and fiction'" (citation omitted)); *see also Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1040 (Fed. Cir. 2006) (Michel, C.J., dissenting from denial of rehearing *en banc*) ("[I]n light of our eight years of experience with [the] application" of the *Cybor* rule of *de novo* review, "I have come to believe that reconsideration is appropriate and revision may be advisable.").

Indeed, claim construction necessarily involves many subsidiary factual determinations, even without the consideration of extrinsic evidence. For instance, claim construction first requires a court to determine the date and field of the invention in light of the evidence presented. *See, e.g., Seal-Flex, Inc. v. Athletic Track & Court Constr.*, 98 F.3d 1318, 1324 (Fed. Cir. 1996) ("The trier of fact must determine whether the invention was completed or whether the inventor was continuing to develop and evaluate the invention When these material facts are at issue, summary disposition is negated."); *see also Lighting Ballast*, 744 F.3d at 1306, 1316 (O'Malley, J., dissenting). It also requires the district court to weigh evidence and make a record of various other threshold assessments, including the state of the art, who qualifies as a person of ordinary skill in the art and how such a person would understand the claims in question. *See* ABA, IPL Section, *A Section White Paper: Agenda for 21st Century Patent Reform* at 43-44 (2010) (listing the facts

underlying claim construction).[7] In addition, claim construction demands a number of factual determinations when parsing "the patent documents," such as analyzing the specification to determine whether it contains embodiments, definitions or references relevant to the claim term, and assessing whether the patent's disclosure affects the plain meaning of the claims. *See United States v. Adams*, 383 U.S. 39, 49 (1966) ("[I]t is fundamental that claims are to be construed in light of the specifications."); *see also CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002) ("[T]he claim term will not receive its ordinary meaning if the patentee acted as his own lexicographer."). Factual determinations are also required to assess whether the patent owner

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[7] *Available at* http://www.americanbar.org/content/dam/aba/administrative/intellectual_property_law/advocacy/white_paper_sept_2010_revision.authcheckdam.pdf. Although not presented to the ABA House of Delegates for adoption as ABA policy, this White Paper sets out the IPL Section's views on patent law reform issues. In it, the Section recommends that at least the following questions should be characterized as findings of fact related to claim construction: (i) who qualifies as a person of ordinary skill in the art; (ii) what was the state of the art at the time of the invention (the scope and content of the prior art); (iii) the differences between the prior art and the claims at issue; (iv) how a person of ordinary skill in the art would understand a claim term; (v) how a claim term is used in the written description portion of the specification of the patent; (vi) how a claim term is used in the prosecution history of the patent (how one of ordinary skill in the art would understand statements made by the applicant during prosecution); (vii) how a claim term is used in the prior art; (viii) what relevant texts, including dictionaries and treatises, say about the meaning of the claim term; and (ix) what experts in the art say about the meaning of a claim term. *Id.* at 34.

disclaimed any claim scope during prosecution and to determine the differences between the prior art and the claimed invention.[8] *See Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003) ("[P]rosecution disclaimer narrows the ordinary meaning of the claim congruent with the scope of the surrender."). This Court has made clear that such preliminary determinations are "matter[s] of fact." *See Great N. Ry. Co. v. Merchs' Elevator Co.*, 259 U.S. 285, 291-92 (1922) (noting that the construction of a contract is a matter of law with a number of underlying factual inquiries); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966) ("While the ultimate question of validity is one of law," obviousness "lends itself to several basic factual inquiries.").

When extrinsic evidence is considered in claim construction determinations, trial courts are tasked with further fact-finding duties. First, courts must perform a gatekeeping role, assessing whether extrinsic evidence such as dictionaries, treatises or expert testimony would assist in the interpretation of the claim term.[9] *See, e.g.*,

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[8] In this case, the district court engaged in such factual inquiries when construing the term "molecular weight." *See Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 723 F.3d 1363 (Fed. Cir. 2013), *cert. granted*, 134 S. Ct. 1761 (2014). Specifically, the district court determined the field of the invention and defined the level of ordinary skill in the art. *Id.* at 1367-70. The court also considered whether the specification provided evidence in favor of a particular construction of the claim phrase at issue and weighed allegations that the patent owner made inconsistent statements during prosecution. *Id.*

[9] The district court in this case relied upon the testimony of Petitioners' expert, Dr. Grant, in making its determination. *Teva Pharms.*, 723 F.3d at 1369-71.

Neomagic Corp. v. Trident Microsystems, Inc., 287 F.3d 1062, 1074 (Fed. Cir. 2002) ("[O]n the record before us we think that this [claim construction] matter can only be resolved by further evidentiary hearings, including expert testimony."). If such extrinsic evidence is admitted, courts must assess its weight, determine witnesses' (including expert witnesses') credibility and balance controverting evidence. *See Lighting Ballast*, 744 F.3d at 1316 (O'Malley, J., dissenting).

Moreover, claim construction hearings often involve the development of a detailed factual record, including the receipt of live testimony. *Markman* proceedings—roughly equivalent to a bench trial on a specific issue—are often held "live with argument and testimony, sometimes covering several days." *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 659 F.3d 1369, 1374 (Fed. Cir. 2011) (O'Malley, J., dissenting from denial of rehearing *en banc*). By providing a forum for "weighing all the [intrinsic and extrinsic] evidence bearing on claim construction and assess[ing it] accordingly," *Phillips*, 415 F.3d at 1319, *Markman* hearings provide the basis for the factual findings that necessarily underpin a district court's claim construction.

II. Pursuant to Federal Rule of Civil Procedure 52(a)(6), Findings of Fact Must Not Be Set Aside Unless Clearly Erroneous

Pursuant to Federal Rule of Civil Procedure 52(a)(6), a district court's "[f]indings of fact" cannot be overturned on appeal unless they are deemed "clearly erroneous." Fed. R. Civ. P. 52(a)(6). Rule 52 applies to appellate review of *any* findings of fact made without a jury, regardless of the kind of

proceeding or the type of evidence involved. *See, e.g., United States v. U.S. Gypsum Co.*, 333 U.S. 364, 394-95 (1948) (Rule 52(a) applies to "all actions tried upon the facts without a jury."); *Pullman-Standard v. Swint*, 456 U.S. 273, 287 (1982) (Rule 52(a) "does not make exceptions or purport to exclude certain categories of factual findings."); *see also Bose Corp. v. Consumers Union of U.S., Inc.*, 466 U.S. 485, 498 (1984) (reiterating that Rule 52(a) "means what it says"). In patent cases, the underlying factual determinations made during claim construction should therefore be reviewed under a "clearly erroneous" standard. *See* Lauren Maida, *Patent Claim Construction: It's Not A Pure Matter of Law, So Why Isn't the Federal Circuit Giving District Courts the Deference They Deserve?*, 30 Cardozo L. Rev. 1773, 1803 (2009) ("Rule 52(a) is an appropriate standard [for factual findings underlying claim construction] because it would ensure that the district court is the first and only trial court.").

Notably, neither *Cybor* nor *Lighting Ballast* grapples with the impact of Rule 52(a). Instead, both opinions characterize claim construction as a purely legal question. As this Court noted in *Markman*, however, claim construction is a mixed issue of law and fact. *Markman*, 517 U.S. at 388. As a hybrid inquiry, claim construction therefore demands a hybrid standard of review: Rule 52(a)'s deferential "clear error" assessment for underlying findings of fact, and *de novo* review for the ultimate issue of claim construction. This tiered review comports with this Court's precedent, which routinely asks appellate courts to distinguish between findings of fact and conclusions of law, and apply a different standard of review to each, on appeal. *See, e.g., Cooper Indus., Inc. v. Leatherman Tool Grp., Inc.*, 532 U.S. 424, 440 n.14 (2001)

(holding that application of the *Gore* test for punitive damages is reviewed *de novo* but noting that the "Court of Appeals should defer to the District Court's findings of fact unless they are clearly erroneous"); *Ornelas v. United States*, 517 U.S. 690, 699 (1996) (holding that "determinations of reasonable suspicion and probable cause should be reviewed *de novo* on appeal," but "findings of historical fact [should] only [be reviewed] for clear error").

This Court's obviousness precedent further supports "clear error" review for findings of fact made during claim construction. In *Graham v. John Deere Co. of Kansas City*, this Court noted that "[w]hile the ultimate question of validity is one of law," obviousness "lends itself to several basic factual inquiries." 383 U.S. at 17. The factual questions this Court identified bear a striking resemblance to the factual questions underlying claim construction, and include: (i) the level of skill in the art, (ii) the scope and content of the prior art and (iii) differences between the prior art and the claims at issue. *See id.* In an obviousness inquiry, these underlying factual determinations are subject to Rule 52(a). *See Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 811 (1986) (per curiam). Those same factual findings should likewise be subject to "clear error" review in the claim construction context.

III. Public and Judicial Policy Considerations Demand Deference to a District Court's Findings of Fact

When the subsection "Setting Aside Factual Findings" was added to Rule 52(a), the drafters of the rule were careful to counsel against *de novo* review of findings of fact:

> [T]he public interest in stability and judicial economy would be promoted by recognizing that the trial court, not the appellate tribunal, should be the finder of facts. To permit courts of appeals to share more actively in the fact-finding function would tend to undermine the legitimacy of the district courts in the eyes of litigants, multiply appeals by encouraging appellate retrial of some factual issues, and needlessly reallocate judicial authority.

Fed. R. Civ. P. 52(a) advisory committee's note (1985 amendment). By rejecting clear error review, the Federal Circuit's decisions in *Cybor* and *Lighting Ballast* have resulted in a reversal of the traditional allocation of labor between trial and appellate courts, a high reversal rate and resulting lack of predictability at the Federal Circuit and longer and more costly litigations. *See* J. Jonas Anderson & Peter S. Menell, *Informal Deference: A Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 Nw. U. L. Rev. 1, 70 (2014) ("The private and social costs of the de novo standard of review manifest in various ways: lower quality decision-making at both the trial and appellate levels, higher costs of litigation greater uncertainty longer case pendency and fewer and delayed settlements." (footnote omitted)); *see also Cybor*, 138 F.3d at 1473-78 (Rader, J., dissenting); *Amgen*, 469 F.3d at 1040 (Michel, C.J., dissenting from denial of rehearing *en banc*). Both decisions should be overruled.

A. District Courts Are Better Positioned to Make Findings of Fact

District courts are better equipped to make findings of fact, and those findings should receive deference on appeal. *See Cooter & Gell v. Hartmarx Corp.*, 496 U.S. 384, 402 (1990) ("Familiar with the issues and the litigants, the district court is better situated than the court of appeals to marshal the pertinent facts and apply the fact-dependent legal standard."); *Salve Regina Coll. v. Russell*, 499 U.S. 225, 233 (1991) ("[D]eferential review of mixed questions of law and fact is warranted when it appears the district court is 'better positioned' to decide the issue." (citation omitted)). The factual findings underlying claim construction are no exception.

"In addition to compromising the care and logic that comes from building a factual record and preparing a reasoned opinion de novo review [requires] an independent review of an anemic record—typically limited to the intrinsic evidence." Anderson & Menell, *Informal Deference*, *supra*, at 69. Indeed, when examining the meaning of a claim, "[t]he district court has the opportunity to see and hear testimony first hand, along with the accompanying gestures, exhibits, charts, and models. This gives the district court a better opportunity to grasp the nature of the invention." Maida, *Patent Claim Construction*, *supra*, at 1797 (footnote omitted); *see also Cybor*, 138 F.3d at 1477 (Rader, J., dissenting) (The "[t]rial judge[] can spend hundreds of hours reading and rereading all kinds of source material, receiving tutorials formally questioning technical experts and deliberating over the claim language."). "[T]he trial court is [therefore] *better*, that is, more accurate, by way of both position and practice, at finding facts

than appellate judges." *Phillips*, 415 F.3d at 1334 (Mayer, J., dissenting) (emphasis in original); *see also Cybor*, 138 F.3d at 1478 (Rader, J., dissenting) (Appellate judges must rely on the "sterile written record" that "can never convey all the nuances and intangibles of the decisional process."); *Lighting Ballast*, 744 F.3d at 1311 (O'Malley, J., dissenting) (*De novo* review "'deprives th[is] court, and the parties, of the accumulated progress and experience of the trial [judge] and leaves us with an expurgated record and generally inferior basis of decision.'" (citation omitted)).

Moreover, abandoning *de novo* review of district court fact-finding poses little risk of disrupting national uniformity in claim construction, as the Federal Circuit has suggested. *See Cybor*, 138 F.3d at 1455 (arguing that *de novo* review will "provid[e] national uniformity to the construction of patent claim[s]"). "[T]he claim construction issues presented in patent cases are mostly fact and case specific," and "will provide little guidance on the words used in different patents." *Lighting Ballast*, 744 F.3d at 1314 (O'Malley, J., dissenting); *see also* 6-18B Donald S. Chisum, *Chisum on Patents* § 18.07[1] at 18-1188 (2014) ("Court decisions interpreting and applying language in particular patent claims cannot create controlling precedent for the interpretation and application of other patents' claims to varying products and processes "). Moreover, even when the same patent is litigated in multiple jurisdictions, district courts have an array of tools, including consolidation, transfer, schedule coordination or even stays, to help avoid inconsistent rulings. Deferring on factual questions to district court determinations thus should not affect the goal of greater national uniformity.

B. *De Novo* Review Has Led to a Lack of Predictability on Appeal

De novo review has also had another deleterious impact: a consistently high reversal rate for district court claim construction decisions at the Federal Circuit. By some estimates, this rate has ranged anywhere from 30-50%. *See* Jay P Kesan & Gwendolyn G. Ball, *Judicial Experience and the Efficiency and Accuracy of Patent Adjudication: An Empirical Analysis of the Case for a Specialized Patent Trial Court*, 24 Harv. J.L. & Tech. 393, 434 (2011) (citing claim construction reversal rates between 40-50%); Maida, *Patent Claim Construction*, *supra*, at 1773 ("The rate of Federal Circuit reversals of district court claim constructions is as high as fifty percent."); David L. Schwartz, *Practice Makes Perfect? An Empirical Study of Claim Construction Reversal Rates in Patent Cases*, 107 Mich. L. Rev. 223, 240 (2008) (citing a 38.8% rate for "cases with at least 1 wrongly construed term").[10] Indeed, even after the Federal Circuit's *en banc* decision in *Phillips v. AWH Corp.* in 2005, which provided a clearer framework for appellate review of claim construction and led to fewer reversals overall, the reversal rate has remained notably high, particularly when compared to other areas of federal practice. *See, e.g.*, Anderson & Menell,

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[10] *See also* Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, 9 Lewis & Clark L. Rev. 231, 233, 236 (2005) (citing a 34.5% reversal rate); Christian A. Chu, *Empirical Analysis of the Federal Circuit's Claim Construction Trends*, 16 Berkeley Tech. L.J. 1075, 1112 (2001) (citing a reversal rate as high as 51% for summary judgment decisions on claim construction).

Informal Deference, *supra*, at 6 (noting that "[t]he reversal rate on a per-case basis" after *Phillips* is 31.6%); Ted Sichelman, *Myths of (Un)Certainty at the Federal Circuit*, 43 Loy. L.A. L. Rev. 1161, 1174 (2010) ("[O]n an issue-by-issue basis, the Federal Circuit reverses lower court claim construction rulings much more than most other issues.").

This high rate of reversal has also created a perception among litigants that claim construction is often dependent on the particular panel a litigant receives. *See* Donald R. Dunner, *A Retrospective of the Federal Circuit's First 25 Years*, 17 Fed. Cir. B.J. 127, 130 (2008) (noting many believe "that Federal Circuit predictability is not what it should be and that its decisions are often panel-dependent and result-oriented"); R. Polk Wagner & Lee Petherbridge, *Is the Federal Circuit Succeeding? An Empirical Assessment of Judicial Performance*, 152 U. Pa. L. Rev. 1105, 1112 (2004) ("Our findings indicate that claim construction at the Federal Circuit is panel dependent."); *see also Retractable Techs.*, 659 F.3d at 1370 (Moore, J., dissenting from denial of rehearing *en banc*) ("Commentators have observed that claim construction appeals lead[] to frustrating and unpredictable results."); Kesan & Ball, *Judicial Experience*, *supra*, at 413 (noting that "the composition of the panel hearing the case can have an impact on the decision"). Increasing the level of deference afforded to district courts' factual findings would alleviate these concerns by focusing Federal Circuit review on the legal aspects of claim construction, and allowing the Court of Appeals to provide "practical guidance [to patent drafters and litigants] regarding how [a] claim construction dispute might be resolved." *Lighting Ballast*, 744 F.3d at 1302 (O'Malley, J., dissenting).

C. *De Novo* Review Has Increased the Length and Cost of Patent Litigation

Under *Cybor*, "'the trial court's claim interpretation provides no certainty at all, but only opens [up] the bidding.'" *Lighting Ballast*, 744 F.3d at 1313 (O'Malley, J., dissenting) (citation omitted). In fact, under the current system of *de novo* review:

> To get a certain claim interpretation, parties must go past the district court's *Markman* proceeding, past the entirety of discovery, past the entire trial on the merits, past post trial motions, past briefing and argument to the Federal Circuit—indeed past every step in the entire course of federal litigation, except Supreme Court review.

Cybor, 138 F.3d at 1476 (Rader, J., dissenting). Indeed, as noted above, by some estimates, in 30-50% of cases, even Federal Circuit review has not ended the story. In those cases, the Court of Appeal's reinterpretation of the claims typically leads to a remand for new proceedings, which can involve further discovery, renewed motion practice and a new trial. *See* Maida, *Patent Claim Construction*, *supra*, at 1784 (a *de novo* standard can lead to duplicative proceedings, and often "requires a second trial on the issue of infringement"); *see also, e.g., AFG Indus., Inc. v. Cardinal IG Co.*, 375 F.3d 1367, 1374-75 (Fed. Cir. 2004) (Newman, J., dissenting) (remanding "for the third time on claim construction").

This tortuous system upsets the parties' *ex ante* expectations of predictability in the enforcement of patents, "and undo[es] a tremendous amount of work in the process." *Lighting Ballast*, 744 F.3d at 1310 (O'Malley, J., dissenting); *see also* Maida, *Patent Claim Construction*, *supra*, at 1792-93 ("[S]ome suggest that perhaps [district] judges should not even bother to 'waste their limited resources' on a thorough claim construction analysis." (citation omitted)). Moreover, by postponing certainty until the end of the litigation process, *de novo* review "creates greater incentives for losing parties to appeal, thus discouraging settlements." *Lighting Ballast*, 744 F.3d at 1313 (O'Malley, J., dissenting); *See also* Chu, *Empirical Analysis of the Federal Circuit's Claim Construction Trends*, *supra*, at 1120 (*de novo* review means parties have every incentive to appeal and no incentive to settle, regardless of the outcome at trial). These delays necessarily increase the length and cost of litigation, and require businesses to operate in uncertainty for longer periods of time. *See* Maida, *Patent Claim Construction*, *supra*, at 1798 (calling *de novo* review "an economically costly standard"); Schwartz, *Practice Makes Perfect? supra*, at 226 ("Unpredictability [in appellate review of claim construction] raises legal costs.")

With the Federal Circuit becoming "the real center stage," *de novo* review also alters the behavior of trial counsel. *Cybor*, 138 F.3d at 1477 (Rader, J., dissenting). In the current regime, "attorneys must devote much of their trial strategy to positioning themselves for the 'endgame' – claim construction on appeal. As the focus shifts from litigating the correct claim construction to preserving ways to compel reversal on appeal, [*e.g.*, making arguments in the alternative], the

uncertainty, cost and duration of patent litigation only increase." *Id.* at 1476; *see also* Kyle J. Fiet, *Comment, Restoring the Promise of* Markman*: Interlocutory Patent Appeals Reevaluated Post-*Phillips v. AWH Corp., 84 N.C. L. Rev. 1291, 1311 (2006) ("Unfortunately, Judge Rader's prediction that the de novo review standard would 'undermine, if not destroy the certainty and predictability sought by *Markman* ' largely has been realized." (first ellipsis in original) (citation omitted)).

For these reasons, this Court should reject the *de novo* standard of review, and hold that findings of fact made during claim construction may be overturned only for "clear error" pursuant to Rule 52(a)(6).

CONCLUSION

For the foregoing reasons, the ABA respectfully submits that this Court should overrule *Cybor* and *Lighting Ballast* and replace the existing *de novo* standard of review for the factual findings underpinning claim construction with a "clearly erroneous" standard of review.

Respectfully Submitted,

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Appendix

APPENDIX — ABA RESOLUTION #302

AMERICAN BAR ASSOCIATION

ADOPTED BY THE HOUSE OF DELEGATES
August 9-10, 2004

RESOLVED, That the American Bar Association recommends that courts apply the following principles in interpreting claim terms in a patent—

--In construing a patent claim term, the ordinary meaning of the claim term to one of ordinary skill in the art as used in the context of the patent shall apply, unless (a) the patentee has acted as his or her own lexicographer, in which case the patentee's definition should control; or (b) there has been a clear disavowal of claim scope, in which case the patentee should be bound by such action. In determining the ordinary meaning of the claim term to one of ordinary skill in the art as used in the context of the patent, the court shall look to dictionaries and similar sources, the specification and the prosecution history;

--While technical dictionaries should be given more weight than general purpose dictionaries, all types of dictionaries and similar sources should be considered;

--In construing or interpreting any disputed portion of a patent claim, courts should not rely on dictionaries and similar sources unless (a) that material has been made part of the record and (b) the parties have had a full and fair opportunity to address, challenge, or rebut that material;

Appendix A

--Courts should not apply a rule of claim construction whereby the specification is the primary source for claim construction such that the range of ordinary meaning of claim language is limited to the scope of the invention disclosed in the specification;

--Courts should not apply a rule of claim construction whereby the claim construction methodologies in the majority and dissent in the now-vacated panel opinion in *Phillips v. AWH Corp.*, 363 F.3d 1207 (Fed. Cir. 2004), are treated as complementary methodologies such that there is a dual restriction on claim scope, and a patentee must satisfy both limiting methodologies in order to establish the claim coverage it seeks;

--Courts should not consider invalidity under, e.g. 35 U.S.C. 102, 103, and 112, when construing claim terms in a patent;

--Courts should apply a rule of claim construction in which the prosecution history is given the same weight as the specification and both are considered in every case when evaluating the meaning of a claim term;

--Trial courts should receive expert testimony at the court's discretion to educate the court on the technology, but expert testimony may not be used to contradict the claim meaning discernable from the dictionaries and similar sources, specification, and prosecution history;

--While the ultimate issue of claim construction should be reviewed de novo, an appellate court should review only by the clearly erroneous standard any underlying findings of fact made by a trial court in connection with construing a claim term.

AMICUS CURIAE BRIEF

No. 13-854

IN THE
Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Writ of Certiorari
To the United States Court of Appeals
For the Federal Circuit

Brief for Amicus Curiae American Intellectual Property Law Association in Support of Neither Party

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QUESTION PRESENTED

Claim construction is a question of law to be decided by the trial court. *Markman v. Westview Instruments*, 517 U.S. 370 (1996). Claim construction requires a determination of what the claims would have meant to a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). This may involve mixed questions of fact and law. *Markman*, 517 U.S. at 377, 388. Rule 52(a)(6) of the Federal Rules of Civil Procedure provides that "[f]indings of fact . . must not be set aside unless clearly erroneous." Did the Federal Circuit err in treating all issues of claim construction as conclusions of law that are subject to *de novo* review, or are certain subsidiary factual issues involved in the construction of patent claims reviewed only for clear error?

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INTEREST OF *AMICUS CURIAE*

The American Intellectual Property Law Association ("AIPLA") is a national bar association of nearly 15,000 members interested in all areas of intellectual property law.[1] AIPLA members include attorneys in private practice and those employed by corporations, universities, and government. AIPLA members represent both owners and users of intellectual property.

AIPLA has no stake in any of the parties to this litigation or in the result of this case, and takes no position on the merits in support of or against any party. Its interest is solely in seeking correct and consistent interpretation of patent law.[2]

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[1] Pursuant to Supreme Court Rule 37.6, the Association states that this brief was not authored in whole or in part by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the Association and its counsel. Specifically, after reasonable investigation, AIPLA believes that (i) no member of its Board or Amicus Committee who voted to file this brief, or any attorney in the law firm or corporation of such a member, represents a party to this litigation in this matter; (ii) no representative of any party to this litigation participated in the authorship of this brief; and (iii) no one other than AIPLA, or its members who authored this brief and their law firms or employers, made a monetary contribution to the preparation or submission of this brief.

[2] Petitioner and Respondent have consented to the filing of this amicus brief.

I. SUMMARY OF ARGUMENT

This amicus brief challenges the Federal Circuit's practice of reviewing all claim construction decisions under a *de novo* standard of review, *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc), including those based on an extensive evidentiary record, *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 659 F.3d 1369 (Fed. Cir. 2011). This practice has been assailed by segments of the bar, industry, innovators, and by some district courts as increasing uncertainty in patent infringement cases. It is cited as contributing to the high rate of appeals taken in patent infringement cases, to an inability to predict the outcome of patent cases short of Federal Circuit review, and to anecdotal dissatisfaction by district judges for patent cases. Moreover, AIPLA respectfully submits that it is inconsistent with the requirements of Fed. R. Civ. P. 52(a)(6) that no finding of fact may be disturbed except for clear error. Nonetheless, the Federal Circuit recently confirmed its adherence to this practice of *de novo* review in *Lighting Ballast Control LLC v. Philips Electronics North America Corp.*, 744 F.3d 1272 (Fed. Cir. 2014) (*en banc*), on *stare decisis* and policy grounds.

The parties present this Court with starkly contrasting positions that AIPLA believes take too coarse a view of this issue. Petitioners appear to contend that all issues of claim construction should be considered "findings of fact" subject to review only for clear error under Fed. R. Civ. P. 52(a)(6). Respondents do not go to the opposite extreme of contending that no deference should ever be given on

claim construction. Nonetheless, Respondents contend that regardless whether the standard of review is clear error or *de novo* review, the outcome in this case would be the same.

AIPLA respectfully submits that the correct approach lies somewhere in between. Respondents acknowledge that the district court credited Teva's expert witness's testimony. Respondents' Opposition to Petition at 22. This alone establishes an evidentiary basis for some finding of fact, provided the testimony is properly admitted.

As this Court recognized in *Markman*, claim construction is a "mongrel practice." 517 U.S. at 378. AIPLA believes that the ultimate question of claim construction remains a question of law for the trial court to decide and for the appeals court to review *de novo*. Certain subsidiary issues based on the intrinsic evidence are properly considered questions of law that are reviewed *de novo*. Yet, claim construction may involve mixed questions of fact and law. Those subsidiary issues are based on extrinsic evidence and properly should be considered findings of fact subject to review only for clear error. In keeping with this Court's decision in *Markman* and Title 35, United States Code, these findings of fact must be consistent with the language of the claims, the specification, and the prosecution history as understood by one of ordinary skill in the relevant art. While these intrinsic sources serve the public notice function of a patent and are subject to *de novo* review. Nonetheless, if claim construction involves issues of historical fact, or findings based on extrinsic evidence, which could involve the testimony

of lay or expert witnesses, or the interpretation of printed publications or patents that are not part of the intrinsic record, AIPLA believes that these limited subsidiary factual findings should be reviewed only for clear error.

This hybrid approach—reviewing findings based on extrinsic evidence for clear error, and reviewing conclusions based on intrinsic evidence de novo—was asserted by the United States and others in *Lighting Ballast*. The Federal Circuit en banc rejected the approach, adhering to *Cybor's de novo* review on policy grounds based on *stare decisis*. Yet, policy is not a sufficient answer to the legal requirements of Rule 52(a)(6). Whether any alternative standard of review is better or easier to implement is not the question. Fed. R. Civ. P. 52(a)(6) mandates the standard of appellate review. The decision was Congress's to make in promulgating Rule 52, and the Federal Circuit is not free to perpetuate a different standard on *stare decisis* grounds.

AIPLA proposes parsing conclusions based on intrinsic evidence, which are reviewed *de novo*, from findings of fact based on extrinsic evidence, which are reviewed only for clear error. Although this distinction was disputed by the *en banc* majority in *Lighting Ballast*, this approach provides a number of benefits. First, it is simple and clear. Second, it complies with the requirements of Fed. R. Civ. P. 52(a)(6) and adheres closely to this Court's guidance in *Markman*. Third, it preserves the paramount role of the intrinsic evidence in providing public notice of the scope of the patent.

If the district court hears extrinsic evidence that is relevant to claim construction and makes factual findings based on it, these findings of fact are reviewed for clear error. The district court cannot, however, rely on such evidence if it would contradict the intrinsic record, which is critical to the public notice function of a patent. AIPLA respectfully submits that this clear and simple rule would provide substantial guidance to the district courts, comply with controlling authority, and strike an appropriate balance between the trial and appeals court in crediting their respective roles in claim construction.

II. ARGUMENT

A. The Federal Circuit's *Cybor* Standard of *de novo* Review of Claim Construction Fails to Comply with Fed. R. Civ. P. 52 (a)(6)

In *Cybor*, the Federal Circuit ruled that claim construction "is a purely legal question," and "we review claim construction *de novo* on appeal including any allegedly fact-based questions relating to claim construction." 138 F.3d at 1456. This standard of review accords no deference to the trial court's findings of fact. It applies even when the determination of fact is based on extrinsic evidence, and even when it is based on live testimony. *Id.* The Federal Circuit has adhered to this rule even as to findings of fact based on testimony taken at a live evidentiary hearing. *Retractable Techs.*, 659 F.3d at 1374.

The Federal Circuit's *Cybor* holding is founded on a misapprehension of this Court's decision in *Markman II*,[3] is misaligned with this Court's treatment of findings of fact that are subsidiary or collateral to legal conclusions in other subject matter areas of the law, and is inconsistent with the sound and efficient administration of justice.

The Federal Circuit has addressed this issue repeatedly. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995) (*en banc*) ("*Markman I*"); *Cybor*; *Lighting Ballast*. The Federal Circuit in *Cybor* interpreted this Court's *Markman II* decision as holding that claim construction is entirely legal. *Cybor*, 138 F.3d at 1456. Although acknowledging that this Court neither addressed nor decided the appropriate appellate standard of review, the *en banc* Federal Circuit, over vigorous dissent, held that *de novo* review applies to all issues of claim construction.

Following sixteen years of debate over the appropriate standard of review of claim construction, the Federal Circuit recently confirmed the *Cybor* standard of *de novo* review in its *Lighting Ballast* decision, It did so not because of binding legal precedent, or facts establishing that the *Cybor* standard is superior to the alternatives. It did so on *stare decisis* grounds, citing the policies of national uniformity, consistency, and finality. Yet, these policies fail to address the lack of uniformity, lack of

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[3] *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996) ("*Markman II*").

consistency, or lack of finality flowing from not knowing what a patent claim means until after the Federal Circuit has issued its mandate or this Court has denied *certiorari*. More important, even were these perceptions accurate—and they are vigorously disputed in some quarters—they cannot trump the legal requirements of Fed. R. Civ. P. 52(a)(6). Even were the Federal Circuit correct that *Cybor* has not proved unworkable and that any alternative lacks doctrinal consistency in isolating fact from law, *Lighting Ballast*, 744 F.3d at 1283, these policy considerations cannot trump Congress's statutory authority to require that findings of fact not be overturned except for clear error. Fed. R. Civ. P. 52(a)(6).

B. Claim Construction Falls Between a Pristine Legal Standard and a Simple Historical Fact

Cybor perceived that this Court in *Markman II* held that claim construction is a pure question of law. *Cybor*, 138 F.3d at 1455-56. Rather, this Court held to the contrary. Although this Court affirmed the Federal Circuit's *Markman I* decision, it expressly recognized that claim construction is often a mixed question of fact and law, a "mongrel practice." *Markman II*, 517 U.S. at 378. It "falls somewhere between a pristine legal standard and a simple historical fact." *Id.* at 388 (quoting *Miller v. Fenton*, 47 U.S. 104, 114 (1985)). *See also Cybor*, 138 F.3d at 1464 (Mayer, C.J., joined by Newman, J., concurring) (stating that this Court in *Markman* "chose not to accept [the Federal Circuit's]

formulation of claim construction: as a pure question of law to be decided de novo in all cases on appeal").

Claim construction inherently involves the determination of mixed fact/law questions. The question for this Court is the degree of each. The legal components include determinations based on the intrinsic evidence, including: (a) the common, ordinary meaning of the words used in the claims; (b) other words used in other claims in the patent; (c) the specification; (d) the prosecution history; and (e) other patents and printed publications that are cited in the specification and prosecution history, and are part of the intrinsic evidence. These determinations are made as a matter of law, are not subject to Fed. R. Civ. P. 52(a)(6), and are reviewed *de novo*.

In construing claims, a court is not required to accept any extrinsic evidence. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1318-19. If it does accept extrinsic evidence, the extrinsic evidence must not contradict the intrinsic evidence, *id.*, since doing so would undermine the public notice function of the patent. Nonetheless, in appropriate cases in which the court does accept extrinsic evidence, findings of fact may be based on the extrinsic evidence, including: historical facts; the credibility of lay witnesses; expert testimony on relevant issues; and information from other patents, printed publications, and other references that were not cited in the specification and prosecution history and, therefore, are not part of the intrinsic record. To the extent that the district court properly admits and relies upon extrinsic

evidence in making findings of fact, these findings should be reviewed only for clear error.

There are relatively limited and circumscribed instances where a district court may use extrinsic information to make "findings of fact" subject to the requirements of Fed. R. Civ. P. 52 (a)(6). This is entirely consistent with this Court's holding in *Markman II*. Because legal issues dominate the analysis, claim construction is an issue of law for the judge and not for the jury to decide. Because the intrinsic evidence serves a vital public notice function and is equally accessible to the trial and appeals courts, *de novo* review of determinations based on the intrinsic evidence is appropriate. Subject to Fed. R. Civ. P. 52(a)(6), however, any findings of fact made by the district court based on extrinsic evidence are reviewed only for clear error.

C. *Markman II* Did Not Resolve the Standard of Appellate Review

The dissent in *Cybor* noted that the Supreme Court in *Markman II* "did not address [the standard of] appellate review of claim construction." *Cybor*, 138 F.3d at 1473 (Rader, J., dissenting). Rather, the issue before this Court in *Markman II* was whether the construction of patent claims should be done exclusively by judges, or whether the Seventh Amendment of the U.S. Constitution mandates that the jury has a role in this process. This Court recognized that allocating all issues of construction to judges promotes uniform treatment of a given patent. *Markman II*, 517 U.S. at 390. Nonetheless,

this Court did not address the allocation of responsibility between the trial and appellate courts in the claim construction process.

The Federal Circuit in *Cybor*, however, interpreted *Markman II*'s silence on the standard of review issue as empowering the Federal Circuit to review all subsidiary claim construction issues *de novo*. The Federal Circuit *en banc* majority believed that, by not changing or even addressing the standard of appellate review, the Supreme Court supported *Markman I*'s conclusion that claim construction is a purely legal issue subject to *de novo* review. *Cybor*, 138 F.3d at 1451, 1456. The *Cybor* concurrence, however, disputes this conclusion. *Id.* at 1464 (Mayer, C.J., joined by Newman, J., concurring) ("Even a cursory reading of [*Markman II*] indicates that the Court meant to determine who should interpret the claims, without mandating a standard of appellate review to be used in all circumstances.").

D. The District Court's Findings of Fact on Circumscribed Subsidiary Issues Should Be Reviewed Only for Clear Error

For the circumscribed instances where findings of fact should be reviewed only for clear error, there is no reason for the appellate review of such issues on claim construction to be treated differently than other mixed questions of fact and law. There are numerous examples where deference is accorded to underlying findings of fact, even where

the ultimate question is an issue of law which the appellate court reviews *de novo*. Obviousness is one such example. [4]

E. Findings of Subsidiary Fact in Mixed Questions Are Uniformly Subject to Deference on Appellate Review

Other examples include determining compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph,[5] the on-sale bar,[6]

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[4] "A determination of obviousness under 35 U.S.C. § 103 is a legal conclusion involving factual inquiries." *Kolmes v. World Fibers Corp.*, 107 F.3d 1534, 1541 (Fed. Cir. 1997). The Federal Circuit reviews the ultimate legal determination of obviousness without deference, and reviews the underlying factual inquiries for clear error. *See In re Huang*, 100 F.3d 135, 138 (Fed. Cir. 1996).

[5] Enablement is a question of law reviewed *de novo*, but may involve subsidiary questions of fact. *Union Pac. Res. Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 690 (Fed. Cir. 2001) ("Enablement is a question of law reviewed by this court independently and without deference."); *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) ("Enablement . is a question of law which we independently review, although based upon underlying factual findings which we review for clear error.") (quoting *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991)).

[6] The determination of whether an invention was placed on sale more than one year before a patent application covering the invention was filed is a legal question based on factual inquiries. The Federal Circuit stated, "The ultimate determination that a product was placed on sale under section 102(b) is a question of law, based on underlying facts. We review the ultimate determination *de novo*, but any subsidiary

inventorship,[7] and likelihood of confusion in a trademark case.[8]

Whether a patent contains an enabling disclosure is ultimately a question of law based on underlying findings of fact whether the written description is sufficient to enable a person of ordinary skill in the art to make and use the invention without undue experimentation. *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195 (Fed. Cir. 1999).

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fact findings must be reviewed, in this case, for clear error." *Ferag AG v. Quipp, Inc.*, 45 F.3d 1562, 1566 (Fed. Cir. 1995).

[7] Whether an individual is truly an inventor is a legal conclusion based upon factual inquiries. *Sewell v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994) (inventorship is a question of law, reviewed *de novo* on appeal, with "any facts found in reaching an inventorship holding . reviewed for clear error"). This court reviews a jury's findings of fact as to any contribution by a purported inventor to any claim of the patent under a deferential "substantial evidence" standard, and then decides *de novo* whether that rises to the level of inventorship. *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998).

[8] "Likelihood of confusion under section 2(d) is determined as a matter of law, on the factual record." *In re Shell Oil Co.*, 992 F.2d 1204, 1206 (Fed. Cir. 1993). "On appeal to this court the Board's conclusion is given *de novo* review as to the ultimate question of likelihood of confusion, and the factual findings on which this conclusion is premised are reviewed for clear error." *Id.; see also Century 21 Real Estate Corp. v. Century Life of Am.*, 970 F.2d 874, 876 (Fed. Cir. 1992) ("This court reviews the Board's fact finding under the clearly erroneous standard. The Board's conclusions regarding confusing similarity, however, are questions of law, which this court reviews de novo.").

While the ultimate question of law is reviewed *de novo*, the findings of fact are accorded deference and reviewed only for clear error. These findings of fact are reviewed under the "substantial evidence" standard for jury trials[9] and proceedings in the U.S. Patent and Trademark Office,[10] and under the "clearly erroneous" standard when made by a court.[11]

The ultimate issue of claim construction is the understanding of a person of ordinary skill in the pertinent art at the time the application was filed. *Phillips*, 415 F.3d at 1313; *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. ___ (2014), slip op. at 8-9 (June 2, 2014). Although all issues of claim construction are determined by the court, *Markman II*, 517 U.S. 370, underlying findings of fact based on extrinsic evidence are entitled to deference on appellate review.

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[9] *Glasser v. United States*, 315 U.S. 60, 80 (1942); *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1309-10 (Fed. Cir. 2009).

[10] *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000).

[11] Fed. R. Civ. P. 52(a)(6) ("Findings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility."); *see generally* Kevin Casey, Jade Camero & Nancy Wright, *Standards of Appellate Review in the Federal Circuit: Substance and Semantics*, 11 FED. CIR. BAR J. 279 (2002).

F. Although the Appeals Court is Equally Suited to Review Conclusions Based on Intrinsic Evidence, The District Court Is Better Situated to Make Findings of Fact Based on Appropriate Extrinsic Evidence

Institutional considerations also support that deference is appropriate in reviewing subsidiary findings of fact based on extrinsic evidence. The Federal Circuit is equally capable of reviewing conclusions based on the intrinsic evidence which is equally available to the trial and appeals courts. Thus, *de novo* review of conclusions based on the intrinsic evidence is appropriate. Yet, the Federal Circuit's review is limited to a written record and constrained by time and page limits. The trial judge, in contrast, has greater latitude in case management. The trial judge has more flexibility to study the relevant source materials, to receive technology tutorials, and, in appropriate cases, to hear testimony from lay witnesses and experts. This extrinsic evidence is subject to the paramount limitation that it cannot be "clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history." *Phillips*, 415 F.3d at 1318 (quoting *Key Pharm. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998)). Nonetheless, where live testimony is presented, the trial judge has the opportunity to observe each witness and to assess their credibility. These institutional advantages

support deference to the trial court's findings of fact based on this extrinsic evidence.

When the Federal Circuit substitutes its view of the extrinsic evidence for view of the trial court, it deprives litigants of important substantive and procedural protections that the trial court is in a unique position to provide. *Id.* This Court has cautioned appellate courts to defer "when it appears that the district court is 'better positioned' than the appellate court to decide the issue in question." *Salve Regina Coll. v. Russell*, 499 U.S. 225, 233 (1991). *Cybor* violates this principle. By denying the district court its traditional role as a trier of fact, and by appropriating that role to itself, the Federal Circuit's approach fails to account for the fact that the district court is in a better position to decide these fact issues based on the extrinsic evidence in the first instance.

In this regard, *Cybor* is inconsistent with sound judicial administration. *Cybor* may or may not undermine the benefits of certainty and predictability promised by *Markman II*. *De novo* review encourages the losing party to appeal. Empirical evidence suggests that the Federal Circuit's reversal rate on claim construction issues is substantially higher than that of other circuits generally, and higher than the Federal Circuit's on other issues. Litigants' perceptions that an appellate panel may reach a different result drives unnecessary appeals and increases unpredictability.

"[T]he current *Markman I* regime means that the trial court's early claim interpretation provides

no early certainty at all, but only opens the bidding. [A] *de novo* review of claim interpretation is postponed the point of certainty to the end of the litigation process. " *Cybor*, 138 F.3d at 1476 (Rader, J., dissenting). *Cybor* fosters wasteful, expensive litigation and encourages litigants to pursue unnecessary appeals, consuming trial as well as appellate court resources.

Patent infringement and invalidity claims are often tried on claim constructions that are later reversed on appeal. This wastes time and resources not only of the parties but also of the court and jurors. The cynical adage that "we do not have sufficient time to do it right once but we always have time to do it twice" seems apt. A second trial based on a claim construction modified on appeal is wasteful. Litigants with limited resources can ill-afford a second trial and may be forced to capitulate. The uncertainty of claim construction tends to prolong already expensive litigation creating negotiating leverage for litigants asserting weak positions on the merits. Further, patents are often highly technical documents, written for and interpreted by those of skill in the art, frequently using jargon, technical short-hand or abbreviated discussions, which may require extrinsic interpretation to properly interpret the scope of their claims.

And these problems cannot easily be remedied by intermediate appellate review of claim construction decisions. Interlocutory appeal of claim construction is not available at this time. The district courts consistently decline certification of

such appeals. And the Federal Circuit consistently declines to exercise jurisdiction over them.

Review of findings of fact based on extrinsic evidence only for clear error would provide greater certainty and predictability. Although this standard would not affect all claim construction decisions and may in fact affect a relatively small number of them, the Federal Circuit may benefit from a reduction in the number of appeals taken as well as a reduction in the number of issues presented when an appeal is taken.

Reversing *Cybor* will not disturb the judge's role as the final arbiter of claim construction. The Federal Circuit would defer to district court findings of fact based on appropriate extrinsic evidence and still review the ultimate claim construction *de novo*. Where a district court has committed clear error, the Federal Circuit would remain able to rectify the claim construction, while maintaining reasonable consistency across district court decisions.

The Federal Circuit and this Court will continue to guard against the risk that extrinsic evidence "will be used to change the meaning of claims in derogation of the 'indisputable public records consisting of the claims, the specification and the prosecution history,' thereby undermining the public notice function of patents." *Phillips*, 415 F.3d at 1318-19 (quoting *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1578 (Fed. Cir. 1995)); *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985); *Merck & Co. v. Teva*

Pharm. USA, Inc., 347 F.3d 1367, 1371 (Fed. Cir. 2003).

III. CONCLUSION

AIPLA respectfully requests that this Court conform the appellate review of district court findings of fact subsidiary to claim construction with the review of other mixed questions of law and fact. AIPLA respectfully submits that findings of fact based on the extrinsic evidence should be reviewed only for clear error. By deferring to the trial court on this limited scope of fact-finding, certainty and predictability would be enhanced. Litigants would know that they can rely on the district court's findings of fact. And the Federal Circuit would retain its role as the statutory arbiter of the law.

Respectfully submitted,

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Petitioners,

v.

SANDOZ, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* THE FÉDÉRATION INTERNATIONALE DES CONSEILS EN PROPRIÉTÉ INTELLECTUELLE (FICPI) IN SUPPORT OF NEITHER PARTY

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CORPORATE DISCLOSURE STATEMENT

Counsel for The Fédération Internationale Des Conseils En Probriété Intellectuelle as amicus curiae ("FICPI") certifies the following:

1. The full name of every party of amicus represented by me is:

   Fédération Internationale Des Conseils En Propriété Intellectuelle.

2. FICPI submits this brief *amicus curiae* and has no interest in the outcome of the case.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   None.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

   Eaton & Van Winkle LLP; Maxim H. Waldbaum, Esq.; Robert D. Katz, Esq.

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I. STATEMENT OF INTEREST[1]

The Fédération Internationale Des Conseils En Propriété Intellectuelle ("FICPI") submits this brief as *amicus curie* in support of neither party.

Established in 1906, FICPI is a Switzerland-based international and non-political association of approximately 5,000 intellectual property attorneys from over eighty countries, including the United States. Its members are in private practice, and their clients include individual inventors as well as large, medium and small companies, universities and research institutes.

One of the members' major roles is to advise inventors in intellectual property matters and secure protection for industrial/intellectual innovation. FICPI supports predictable, balanced global protection of patents, the global harmonization of substantive patent law, and the interests of inventors and the U.S. Patent and Trademark Office (the "PTO") in recognizing a fair scope of patent protection consistent with the claimed invention. FICPI recognizes that the instant case has significant potential to impact the validity and claim scope of U.S. patents.

Because FICPI is largely comprised of patent practitioners representing both foreign and domestic inventors and corporate entities, universities and research institutes, FICPI is poised to give the court the

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1. No counsel for any party authored this brief in whole or in part, and no person or entity, other than *amicus curiae*, its members, or its counsel made any monetary contribution to its preparation or submission. Counsel for all parties have consented to the filing of this brief.

perspective of the international patent community. In this vein, FICPI desires to ensure that its members' clients are afforded fair opportunities with respect to patenting their inventions in the United States and protecting those inventions as economically and effectively as possible.

II. INTRODUCTION

On March 31, 2014, this court granted the petition for a writ of certiorari limited to the question presented by the petition:

> Rule 52(a) of the Federal Rules of Civil Procedure provides that in matters tried to a district court, the court's '(f)indings of fact... must not be set aside unless clearly erroneous. The question presented is as follows: Whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel explicitly did in this case), or only for clear error, as Rule 52(a) requires.

III. SUMMARY OF ARGUMENT

In the proceeding below before the Court of Appeals for the Federal Circuit, defendants in consolidated patent infringement actions appealed from the district court's judgment which held that infringement had occurred for various claims of the nine patents-in-suit asserted by the plaintiff, now petitioner (Teva), and from the trial court's holding of invalidity of several patents for indefiniteness, non-enablement and obviousness.

More importantly, the Federal Circuit confirmed its prior ruling in *CyborCorp. v. FAS Techs., Inc.*, 138 F 3d 1448 (Fed. Cir. 1998), that the court had the right to review a trial court's decisions on claim constitution *de novo* without any concern for the substantial work on factual issues and mixed questions of fact and law undertaken by the trial court.

The ruling in Cybor relied heavily on *Markman v. Westview Instruments, Inc.*, 52 F. 3d 967, 977 (Fed. Cir. 1995)("*Markman I*"). However, *Markman I* was not the final word on the issue of claim construction as a matter only of law and the courts' reasoning left the door open for further interpretation. In *Markman I*, the Federal Circuit stated that appellate courts do not have the extensive opportunity to make factual determinations as part of its analysis of whether claim construction itself is a legal issue. *Markman I*, 52 F. 3d at 977, *citing, Read Corp. v. Portec, Inc.*, 970 F. 2d 816 (Fed. Cir. 1992); *Intellicall, Inc. v. Phonometrics, Inc.*, 952 F. 2d 1384 (Fed. Cir. 1992); *Unique Concepts, Inc. v. Brown*, 939 F. 2d 1558 (Fed. Cir. 1991); *Specialty Composites v. Cabot Corp.*, 845 F. 2d 981 (Fed. Cir. 1988).

Markman was later brought before the Supreme Court on appeal and the standard stated in the Federal Circuit decision was more closely analyzed. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996) ("*Markman II*"). The Supreme Court reviewed past attempts to characterize construction of a patent claim as a matter of fact or law and concluded that it is a hybrid:

> The "substance of the common-law right" is, however, a pretty blunt instrument for drawing

> distinctions. We have tried to sharpen it, to be sure, by reference to the distinction between substance and procedure. [...] We have also spoken of the line as one between issues of fact and law. [...] But the sounder course, when available, is to clarify a mongrel practice (like construing a term of art following receipt of evidence) by using the historical method, much as we do in characterizing the suits and actions within which they rise.

Id. at 378.

The Supreme Court in *Markman II* did not determine that claim construction is a pure matter of law free from factual findings. Rather, the Court pointed out that claim construction is indeed a matter of law but also has factual underpinnings. The Court noted the complexity involved in understanding the meaning of a term used in a claim:

> It is, of course, true that credibility judgments have to be made about the experts who testify in patent cases, and in theory there could be a case in which a simple credibility judgment would suffice to choose between experts whose testimony was equally consistent with a patent's internal logic.

Markman II, 517 U.S. at 389. Internal citations omitted.

The Federal Circuit, in the case at bar as well as in the pending companion case of *Lighting Ballast*, maintains that all claim construction issues are to be reviewed by the Federal Circuit *de novo*. *Lighting Ballast Control LLC v.*

Philips Electronics North America Corp, 744 F. 3d 1272 (Fed. Cir. 2014). The argument to support its holding is set forth in *Lighting Ballast*:

> For the reasons we shall discuss, we apply the principle of *stare decisis*, and confirm the *Cybor* standard of *de novo* review of claim construction, whereby the scope of the patent grant is reviewed as a matter of law. *After fifteen years of experience with Cybor, we conclude that the court should retain plenary review of claim construction, thereby providing national uniformity, consistency, and finality to the meaning and scope of patent claims.* The totality of experience has confirmed that *Cybor* is an effective implementation of *Markman II*, and that the criteria for departure from *stare decisis* are not met.

Lighting Ballast Control LLC, 744 F. 3d at 1277(emphasis added).

Harmonious results, however, do not flow necessarily from *de novo* review of the claim construction rulings of the district courts. Rather, *de novo* review has led to inconsistent precedent because judicial economy restricts the appellate court's ability to have a complete understanding of the trial court record and because the appellate court is unable to weigh all the pertinent evidence and the credibility of the pertinent fact and expert witnesses of the parties with the same time devoted to inquiry by a trial court. Additionally, the Federal Circuit's *de novo* review of the district court's claim construction rulings creates the air of wasted time

and effort by the district court and causes unnecessary expense to the litigants.

IV. ARGUMENT

A. Factual Findings Are the Responsibility of the Trial Court

The *de novo* standard of review by the appellate court disregards the trial court's inherently superior vantage point, role and ability to weigh evidence. Factual underpinnings as a part of claim construction are facts, and therefore must be determined by the trial court. These are clearly questions of fact, not law, even if the questions are made to help interpret a legal document. By viewing claim construction as strictly a matter of law subject to *de novo* review on appeal, the Federal Circuit ignores the realities of the underlying factual inquiries undertaken by trial courts in construing claims. Anil Arora, "*The Federal Circuit's De Novo Claim Construction Review Standard: A Titanic Misjudgment Leads to Uncertainty*," 33 N. Ky. L. Rev. 205, 218 (2006).

Without deference to the fact witnesses and experts testifying in a patent case, a credible evaluation cannot be made. *Markman I*, 52 F. 3d at 389. The findings regarding people of ordinary skill in the art should be undisputed as that of fact. If the underlying evidence happens to come from experts, the resulting determination is no less factual.

In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1041 (Fed. Cir. 2006), then Chief Judge Michel and current Chief Judge Rader acknowledged the

importance of these factual determinations by the trial court, stating:

> Our standard of review of no deference to the trial judge's claim constructions, expressed in *Cybor*, rests upon the premise that claim construction is always a purely legal exercise, devoid of factual content. We have likened claim construction to statutory construction. *I believe that this analogy is open to serious question. [...] It seems to me that the claim construction question often cannot be answered without assessing, at least implicitly, what the average artisan knew and how she thought about the particular technology when the patent claims were written.* To make such determinations, the trial judge necessarily relies upon prior art documents and other evidence concerning the skill of the ordinary artisan at the relevant time. *Indeed, trial judges are arguably better equipped than appellate judges to make these factual determinations, especially in close cases. In such instances, perhaps we should routinely give at least some deference to the trial court, given its greater knowledge of the facts.*

Amgen, 469 F.3d at 1040-41 (emphasis added).

In *Cybor*, and especially with respect to claim construction, Chief Judge Rader argued that the district court has a "potentially superior position" to that of the appellate court. For a complex case requiring extrinsic evidence, the trial court "has tools to acquire and evaluate

evidence that [the Federal Circuit] lacks." *Cybor*, 138 F. 3d at 1477 (dissent of Chief Judge Rader). District court judges can receive tutorials on technology from scientists, question technical experts and test their understanding against other experts, examine the invention on site, and deliberate over the meaning of the claim language *Id.*:

> Trial judges can spend hundreds of hours reading and rereading all kinds of source material, receiving tutorials on technology from leading scientists, formally questioning technical experts and testing their understanding against that of various experts, examining on site the operation of the principles of the claimed invention, and deliberating over the meaning of the claim language. If district judges are not satisfied with the proofs proffered by the parties, they are not bound to a prepared record but may compel additional presentations or even employ their own court-appointed expert. An appellate court has none of these advantages.

The opportunity for extensive factual review in assessing patent claim construction which is available only to the trial court may include assessment of custom and usage in the relevant area for which the patent is registered, assessment of events during prosecution, the level of skill and expertise usual to the area for which the patent is registered and the understanding of skilled artisans at the time of invention. *Id.* at 1478. "A careful functional analysis counsels deference for district court claim interpretations." *Id.* Viewed from the perspective of the district court's traditional fact finding role (in contrast to the role of the appellate court), district courts are better

suited to decide the factually complex issues that often arise in claim interpretation. *Id.* at 1479.

In *Apex Inc. v. Raritan Computer, Inc*, 325 F. 3d 1364, 1375 (Fed. Cir. 2003), and in *NeoMagic Corp. v. Trident Microsystems Inc*, 287 F. 3d 1062, 1070, 75-76 (Fed. Cir. 2002), the Federal Circuit confirmed its ruling in *Cybor* that claim construction is a matter of law and subject to *de novo* review, even though the inquiries underlying claim construction were so unquestionably factual that Federal Circuit had no choice but to remand the cases to the district courts for the further fact finding. "These remands for 'lawfinding' and consideration of expert testimony with regard to its 'helpfulness' illustrate the difficulty of applying the *Cybor* holding with a straight face." William H. Burgess, "*Simplicity at the Cost of Clarity: Appellate Review of Claim Construction and the Failed Promise of Cybor*," 153 U. Pa. L. Rev. 763, 786 (2004).

Another scholar has similarly argued:

> If claim construction involves making factual inquiries, it follows that district court judges are suited for this task. [...] District courts have the ability to devote the time and resources necessary for construing these claims. Claim construction may require testimony from persons of ordinary skill in the art to explain the meaning of terms not ordinarily understood by laypersons and terms with a meaning different from ordinary speech. The district court has the opportunity to see and hear this testimony first hand, along with the accompanying gestures,

> exhibits, charts, and models. This gives the district court a better opportunity to grasp the nature of the invention than the Federal Circuit, which must determine the nature of the invention from oral arguments and portions of the record on appeal. *De novo review is not the proper standard for Federal Circuit review of district court claim constructions that involve factual inquiries, because it allows the Federal Circuit to ignore the district court's better opportunity to understand the claims.*

Lauren Maida, "*Patent Claim Construction: It's Not A Pure Matter of Law, So Why Isn't the Federal Circuit Giving the District Courts the Deference They Deserve?*," 30 Cardozo L. Rev. 1773, 1796-97 (2009)(emphasis added).

The court in *Markman I* also pointed out that district court judges are well suited to decide issue of patent claim construction in view of their "training and discipline" and their ability to perform a "sophisticated analysis of the whole document" and weigh an "expert's proposed definition [so that it] fully comports with the specification and claims [...] to preserve the patent's internal coherence." *Markman I*, 52 F. 3d at 388-90.

Irrespective of the major role of the district court and the training and experience of district court judges regarding issues of claim construction, the appellate court has significantly less information to construe than the district court. Because of the time and briefing limitations inherent in the appellate process, parties typically limit their presentations on appeal to "a few issues controlled by a few passages from the specification or the prosecution

history," which results in less than a complete picture of the factual and legal issues presented for trial. *Cybor*, 138 F. 3d at 1478 (fn5)(dissent). Clearly "a sterile written record can never convey all the nuances and intangibles of the decisional process." *Id.* at 1478.

In contrast, deference to the district court's factual findings in claim construction will foster increased certainty with respect to claim interpretation earlier in the process, particularly in complex cases which, in turn, will encourage earlier settlement and substantial cost savings, a very desirable outcome, particularly for less wealthy parties. Further, such deference will have the salutary effect of making the [district court's] trial on the merits the 'main event,' so to speak, rather than a 'tryout on the road' for what will later be the determinative [appeal to the Federal Circuit]. *Cybor*, 138 F. 3d at 1478. This sort of deference will be consistent with patentees' expectations, including foreign individuals and companies involved in patent-related matters in the United States.

The mission of the appellate court is to assure the proper application of the law to the facts found by the fact finder. The appellate court must give due regard to the district court's opportunity to judge the witnesses' credibility, at the very least, respect and defer to the district court's findings of fact. At the same time it does not mean that the appellate court has to accept all factual findings of the district court. Federal Rule of Civil Procedure 52(a)(6) does not affect or restrict the need to prove the proper application of the law. By Rule 52(a)(6), the appellate court is obligated to review the factual findings of the district court that underlie the determination of claim construction for clear error.

Phillips v. AWH Corp., 415 F. 3d 1303 (Fed. Cir. 2005). That standard applies whether those findings are "based on oral or other evidence." The scope of the review is restricted by the rule.

B. De Novo Review in Claim Construction Violates Federal Rule of Civil Procedure 52(a)(6)

As Question 1 notes, Federal Rule of Civil Procedure 52 (a)(6) expressly states that "factual findings must not be set aside unless clearly erroneous." The Rule also limits the authority of the appellate court:

> [An appellate] court may not, however, independently review the constituent facts or disregard the jury's findings, absent proof that they lack sufficient evidence that "a reasonable mind might accept as adequate to support them.

Cybor, dissent 138 F. 3d at 1465.

There is no reason to treat the appellate review of the factual underpinnings related to claim construction any differently than any other factual determinations. Treating factual underpinnings as a **pure question of law would disregard** that they do encompass factual issues. To be consistent with rule 52(a)(6), the appellate court is allowed to disregard them or set them aside only if there is clear error.

Rulings on the definition of the relevant art, the level of ordinary skill in the art, and issues specific to the underlying proceeding, including the credibility of an expert, are all factual issues that the appellate court should review under a "substantial evidence" standard.

C. *De Novo* Review Causes High Reversal Rates on Appeal

The current system of reviewing a district court's findings on claim construction is an additional disincentive for the economy. In *Markman I*, the Court expressly stated that "[...] treating interpretive issues as purely legal will promote (though not guarantee) intra-jurisdictional uniformity under the authority of the single appeals court," *Markman I*, 52 F. 3d at 391. However, many years of practice since *Markman I* show the opposite result. A review of a number of studies shows that the claim construction reversal rates increased between 25 and 71 percent during the period after *Markman I*, See, e.g., Kimberly A. Moore, *Markman Eight Years Later: Is Claim Construction More Predictable?*, Lewis & Clark L. Rev. 231, 233 (2004); Paul M. Schoenhard, *Reversing the Reversal Rate: Using Real Property Principles to Guide Federal Circuit Patent Jurisprudence*, 17 Fordham Intell. Prop. Media Ent. L. J. 299, 302 (2006). This negative development, in turn, lengthens patent litigation and aggravates its already-high cost. Furthermore, predictability has steadily declined and respect for the patent system has been seriously eroded:

> Duplication of the [district court] judge's efforts in the court of appeals would very likely contribute only negligibly to the accuracy of fact determination at a huge cost in diversion of judicial resources.

Anderson v. City of Bessemer, 470 U.S. 564, 575 (1985).

As the Federal Circuit noted in *Markman I*, the district court's early claim interpretation "provides no early certainty at all, but only opens the bidding." *Cybor*, 138 F. 3d at 1476.

D. De novo Review Does Not Promote Harmonization in Patent Cases

The *de novo* standard of review cannot be justified by the aim of harmonizing the law. Congress enacted the Federal Courts Improvement Act of 1982 and created the Federal Circuit to bring uniformity and consistency to patent law throughout the country. But the Federal Circuit has not succeeded in harmonizing the law in the way that district courts and litigants in patent cases can follow a consistent legal application. And this will not change as long as the outcome of the proceedings depends on which appellate panel the litigants appear before:

> There are still legal questions which are unresolved, partly because judges tend to have different views on how different legal questions should be answered. Furthermore, there are many difficult questions of either fact, or application of law to fact, which are very close questions that could be resolved either way.

George C. Beighly, Jr., *The Court of Appeals for the Federal Circuit: Has it Fulfilled Congressional Expectations?*, 21 Fordham Intell. Prop. Media & Ent. L.J. 671, 728 (2011).

The Federal Circuit's longest-tenured judge, Judge Pauline Newman, criticizes the Federal Circuit's "inability to reach a consensus" and recently said at the Fordham Intellectual Property Law and Policy Conference:

> The Federal Circuit's sharply split decisions on contentious issues such as when software is eligible for a patent suggest that those issues raise policy concerns that Congress is in a better position than judges to resolve, [...].The areas where we have not spoken with one voice, like software patents, are not something you can hand over to any group of judges, even the best patent judges in the system.

Ryan Davis, "*Federal Circuit Judge Says Congress Must Resolve Split Rulings*," Law360, April 24, 2014 (http://www.law360.com/articles/531720/fed-circ-judge-says-congress-must-resolve-split-rulings).

Furthermore, in two recent decisions this Court corrected two Federal Circuit tests that it said were too restrictive. *Octane Fitness LLC v. Icon Health & Fitness, Inc.*, 2014 WL 1672251 (U.S. 2014); *Highmark Inc. v. Allcare Health Mangaement System, Inc.*, 2014 WL 1672043 (U.S. 2014). In one decision, the justices held that judges can award attorneys' fees in a case that merely "stands out from others," rejecting the Federal Circuit's rule that attorney's fees are appropriate only when a case is "objectively baseless" and "brought in subjective bad faith." *Octane*, 2014 WL at 1672251. In the other decision, the Supreme Court ended the Federal Circuit's practice of reviewing *de novo* attorney fee award by district courts and, instead, imposed an abuse of discretion standard. *Highmark*, 2014 WL at 1672043.

Indeed, the Supreme Court recently hinted that it disagreed that the Federal Circuit was best suited to review all fee awards. Chief Justice John Roberts noted

in oral argument that the Federal Circuit has recently had a number of sharply split *en banc* decisions. The Chief Justice commented:

> The Federal Circuit was established to bring about uniformity in patent law, but they seem to have a great deal of disagreement among themselves". District court judges often deal with whether a position is baseless in other types of cases, "so maybe they are more expert than the Federal Circuit.

Ryan Davis, *BREAKING NEWS: High Court Strikes Double Blow Against Patent Trolls*, Law360, April 29, 2014 (http://www.law360.com/appellate/articles/532685).

Both decisions of this Court were unanimous, which suggests that the Federal Circuit failed to fulfill its tasks. The Court's decision to reverse the *de novo* review regarding an attorney fee award confirms the importance of the trial court's ability to hear and weigh the evidence and assess the credibility of witnesses, while *de novo* review of claim construction seems only to multiply proceedings and increase cost. This is especially so since the trial court must conduct a trial or decide a summary judgment motion in order to have a final appealable judgment to get the Federal Circuit to review the district court's claim construction. The Federal Circuit will usually not give interim review on the issue of claim constructions alone.

As a practical matter, *de novo* review has a demoralizing effect on district court judges. They tend to invest less

and less time for a claim construction hearing, let alone the time put into reviewing the oftentimes extensive briefing, when their work will be seen as ignored and disregarded on appeal. Many district court judges wonder why they should spend more than a day or even less on such presentations. The wrong message has been sent to them and should be corrected.

The dissent in *Cybor* aptly noted that a *de novo* standard of review "deprives the [trial] court, and the parties, of the accumulated progress and experience of the trial [observing that] it is mysterious why we choose to self-censor what we will consider on appeal." *Cybor*, 138 F. 3d at 1481. Furthermore, Chief Judge William G. Young of the United States District Court for the District of Massachusetts noted that he was reversed in seven out of the nine patent cases that were appealed to the Federal Circuit. He later lamented his "duty is to predict what [the Federal Circuit is] going to say and follow the law, [but noted he has not had] noticeable success with these matters." R. Carl Moy, *Panel Discussion: High Technology Law in the Twenty-First Century Second Annual High Technology Law Conference*, 21 Suffolk Transnat'l L. Rev. 13 (1997).

Judge Samuel B. Kent of the United States District Court for the Southern District of Texas took a less philosophical stand:

> Frankly, I don't know why I'm so excited about trying to bring this [patent suit] to closure. It goes to the Federal Circuit afterwards. You know, it's hard to deal with things that are ultimately resolved by people wearing propeller

> hats. But we'll just have to see what happens when we give it to them. I could say that with impunity because they've reversed everything I've ever done, so I expect fully they'll reverse this, too.

Kimberly A. Moore, "*Are District Court Judges Equipped to Resolve Patent Cases?*," 15 Harvard J. L. & Tech. 1, 11 (2001), citing, O.I. Corp. v. Tekmar Co., No. 95-CV-113 (S.D. Tex. June 17, 1996).

The Federal Circuit's application of *de novo* of review of trial court's claim construction rulings cannot fulfill the mandate of the Federal Circuit to promote harmonization in law. As one scholar has argued:

> By clinging to an untenable *de novo* standard of review for claim construction, the Federal Circuit has, contrary to its intended function, wrought confusion to the patent marketplace.

Anil Arora, "*The Federal Circuit's De Novo Claim Construction Review Standard: A "Titanic" Misjudgment Leads to Uncertainty*," 33 N. Ky. L. Rev. 205, 218 (2006).

V. CONCLUSION

The role of factual findings in claim construction is fundamental, and this case presents an excellent vehicle to decide Question I in the affirmative for clear error and overrule the decision in *Cybor*. Specifically, for the foregoing reasons, this Court should take the opportunity presented in this case to promulgate a ruling whereby an appellate court must give deference to the factual

findings made by a district court underlying the court's claim construction rulings or any other factual or mixed questions of fact and law regarding claim construction.

Such deference will help bring predictability and avoidance of duplicative effort to the single most important event in a patent infringement action. Doing so will also create substantial cost savings and consistency in the manner in which claim construction rulings are reviewed on appeal. Those salutary effects will support progress in achieving uniformity and clarity in patent law and restore the meaningful nature of trial work.

Respectfully submitted,

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June 16, 2014

AMICUS CURIAE BRIEF

No. 13-854

In The Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.

Petitioners,

v.

SANDOZ, INC., ET AL.

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* FRESENIUS KABI USA, LLC IN SUPPORT OF NEITHER PARTY

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QUESTION PRESENTED

1. Whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel explicitly did in this case), or only for clear error, as Rule 52(a) requires.

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INTEREST OF THE *AMICUS CURIAE*[1]

With the consent of the parties, this brief is filed by *Amicus Curiae*, Fresenius Kabi USA, LLC, which is a global leader in medical technology innovation. *Amicus Curiae* engages in the research and development, design, and manufacturing of medicines and medical products for use in the treatment of various conditions and diseases. *Amicus Curiae*'s business operations include the medical technologies of intravenous specialty and generic pharmaceuticals, technologies for transfusion medicine and cell therapies, infusion systems, clinical nutrition, and related medical devices. Fresenius Kabi has no financial interest in the outcome of this case. Fresenius Kabi seeks an application of the patent laws in a manner that most effectively promotes innovation and most accurately reflects the intent of Congress.

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[1] Pursuant to Supreme Court Rule 37, no counsel for any party authored this brief in whole or in part, and no person or entity other than *Amicus Curiae* made a monetary contribution to the preparation or submission of the brief. Counsel of record for all parties were notified prior to filing and have consented to this filing. Letters of consent have been filed with the Clerk of the Court.

SUMMARY OF THE ARGUMENT

The standard that a district court's claim construction receives plenary review on appeal effectuates the goals set forth by this Court in *Markman v. Westview Instruments, Inc.* of correctness and uniformity in defining the scope of patent rights. The principle of bounded rationality that underpins placing claim construction responsibility with the judge rather than the jury also militates for Court of Appeals *de novo* review of the trial court's claim construction. By declining to cabin the Court of Appeals review, this Court remains most faithful to the legislative mandate of promoting patent law uniformity by preserving the Court of Appeals exclusive intermediate appellate authority.

Moreover, a departure from existing practice may bring unintended consequences. The interpretive canon that claims should be construed so as to sustain their validity if possible subsumes disclosure issues such as the written description, enablement and definiteness requirements under 35 U.S.C. § 112, which impact inventions in medical technology more than other technologies. Because these issues can be fact intensive, medical technology innovation companies will suffer a disproportionate burden under a clear error appellate review.

Furthermore, a new, clear error standard for appellate review of claim construction will unduly elevate expert testimony and result in lengthier and costlier district court proceedings in patent cases

generally. This Court should uphold plenary Court of Appeals review of claim construction, including any supporting factual findings.

ARGUMENT

I. The Experience of *Amicus Curiae* Fresenius Kabi USA, LLC, as a Global Leader in Medical Technology Innovation Suggests that a Departure From the Claim Construction Rubric This Court Set Forth in *Markman v. Westview Instruments, Inc.* is Unnecessary and Would Be Detrimental.

The proper interpretation of a patent claim is paramount in patent cases. *See* Giles Sutherland Rich, *Extent of the Protection and Interpretation of Claims—American Perspectives*, 21 INT'L REV. INDUS. PROP. & COPYRIGHT L. 497, 499 (1990) ("To coin a phrase, the name of the game is the claim."). Despite its critical significance, patent claim construction can be problematic. As this Court knows from its recent consideration in *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120 (2014), claim construction may be implicated by certain patent validity considerations, such as the definiteness requirement under 35 U.S.C. § 112, which pose additional complexities. *See Haemonetics Corp. v. Baxter Healthcare Corp.*, 607 F.3d 776, 783 (Fed. Cir. 2010) ("[B]ecause claim construction frequently poses difficult questions over which reasonable minds may disagree, proof of indefiniteness must meet 'an exacting standard.'" (quoting *Halliburton Energy Servs., Inc. v. M–I LLC*, 514 F.3d 1244, 1249 (Fed. Cir. 2008))).

In his 1982 book, MODELS OF BOUNDED RATIONALITY AND OTHER TOPICS IN ECONOMICS, U.S. Nobel Laureate Herbert A. Simon proposed that decision

makers (irrespective of their level of intelligence) work under three unavoidable constraints: (1) only limited, often unreliable, information is available regarding possible alternatives and their consequences, (2) the human mind has only limited capacity to evaluate and process the information that is available, and (3) only a limited amount of time is available to make a decision. Therefore, even individuals who intend to make rational choices are bound to make satisficing (rather than maximizing or optimizing) choices in complex situations. The cognitive heuristic of satisficing—searching through available alternatives for a satisfactory solution rather than the optimal one—applies no less in patent claim construction.

This understanding was manifest in this Court's holding in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388 (1996) that patent claim construction is within the exclusive province of the trial judge. This Court recognized that the categorization of patent claim construction as a question of law or mixed question of fact/law would not suffice alone to guide the fashioning of an appropriate analytical rubric. In this regard, this Court noted:

> We said in *Miller v. Fenton*, 474 U.S. 104, 114 (1985), that when an issue "falls somewhere between a pristine legal standard and a simple historical fact, the fact/law distinction at times has turned on a determination that, as a matter of the sound administration of justice, one judicial actor is better positioned than another to

> decide the issue in question." So it turns out here, for judges, not juries, are the better suited to find the acquired meaning of patent terms.

Id. This Court thus reasoned that the path forward was to focus on placing the inquiry in the hands of the person best equipped through experience and insight to render a proper claim interpretation.

This wisdom extrapolates to plenary appellate review of patent claim construction. Without the constraint of deference to the district court's factual findings on claim construction, the Court of Appeals is better able to employ its considerable experience and insight to reach the most correct claim interpretation. Moreover, the Court of Appeals has the advantage of a keen facility with the interplay between claim construction, validity, enforceability and enforcement to ensure uniformity in the overall application of the patent laws. These considerations support upholding plenary Court of Appeals review of claim construction, including any supporting factual findings.

A. Medical Technology Patents Would Suffer Distinctly With a Shift Away From the Court of Appeals *De Novo* Review of a District Court's Claim Construction.

In an attempt to better inform this Court's understanding of the various medical technologies that may be affected by creating a new, clear error standard for appellate review of claim construction, *Amicus Curiae* respectfully offers its perspective drawn from composite experiences of *Amicus Curiae*

as a global leader in medical technology research and development, design, and manufacturing of medicines and medical products for use in the treatment of various conditions and diseases. These initiatives include intravenous specialty and generic pharmaceuticals, technologies for transfusion medicine and cell therapies, infusion systems, clinical nutrition, and related medical devices. These experiences reflect the extraordinary breadth of technology in this industry sector and foreshadow the importance of recognizing the grave potential consequences, unintended or otherwise, of any change in claim construction methodology for medical technology and health care.

Fresenius Kabi's products are used to treat critically and chronically ill patients. Fresenius Kabi is part of Fresenius SE, a century old group of health care companies based in Germany and with employees and customers in six continents.

1. The Canon of Claim Construction to Interpret a Patent Claim So As to Preserve Validity Where Possible Subsumes Disclosure Issues Such as the Written Description, Enablement and Definiteness Requirements under 35 U.S.C. § 112, Which Impact Inventions in Medical Technology More Than Other Technologies.

Interpretive canons have been fashioned to facilitate proper patent claim interpretation. One such canon is that claims should be construed so as to preserve validity where possible. *See Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999) (quoting *Whittaker*

Corp. v. UNR Indus., Inc., 911 F.2d 709, 712 (Fed. Cir. 1990) ("[C]laims are generally construed so as to sustain their validity, if possible."); *but cf. Generation II Orthotics, Inc. v. Med. Tech., Inc.*, 263 F.3d 1356, 1365 (Fed. Cir. 2001) ("[C]laims can only be construed to preserve their validity where the proposed claim construction is 'practicable,' is based on sound claim construction principles, and does not revise or ignore the explicit language of the claims."); *Liebel-Flarsheim v. Medrad*, 358 F.3d 898, 911 (Fed. Cir. 2004) ("[U]nless the court concludes, after applying all the available tools of claim construction, that the claim is still ambiguous, the axiom regarding the construction to preserve the validity of the claim does not apply."). Even where this canon of patent claim construction is not explicitly applied, the district courts remain mindful of the doctrinal intersection between proper claim interpretation and issues of validity. *See Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1384 (Fed. Cir. 2001) ("The jurisprudence of claim construction reflects the difficult balance between a patentee's exhortation that courts should read the claims broadly and unlimited to the specific embodiments shown in the specification, and the rule that claims should be construed sufficiently narrowly to preserve their validity.").

In addition to the conditions for patentability of statutory subject matter, utility, novelty and nonobviousness under 35 U.S.C. § 101-103, the patent laws set forth the disclosure requirements of written description, enablement, and definiteness under 35 U.S.C. § 112. The adequacy of a patent applicant's disclosure is a prerequisite to the patent

grant. *See, e.g., Carnegie Mellon Univ. v. Hoffmann-La Roche, Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) ("The written description serves a quid pro quo function 'in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'"(citing *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 922 (Fed. Cir. 2004) (quoting *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002)))).

More particularly, the disclosure requirements of written description, enablement, and definiteness under 35 U.S.C. § 112 provide meaningful limitations on the scope of the patent grant by establishing standards against which the patent claims are measured for support. To this end, these considerations under 35 U.S.C. § 112 are often subsumed into the claim construction analysis even while they constitute separate and distinct bases for the determination of patent validity. Given this interrelationship, assessing the impact of any modification of the claim construction rubric implicates how district courts address 35 U.S.C. § 112 issues. And for the reasons *infra*, a change in the current appellate review of district court claim constructions will affect medical technology patents to a greater extent.

With medical technology inventions, the written description requirement, for example, is often implicated due to the pioneering nature and/or complex nomenclature that innovation in this field of endeavor entails. The inconsistent doctrinal application across different technologies has long

been the focus of scholarly debate. *See, e.g.*, Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1652-54 (2003) ("In biotechnology, however, the doctrine has been applied as a sort of 'super-enablement' requirement, forcing biotech patentees to list particular gene sequences in order to obtain a patent covering those sequences. The written description doctrine as currently applied is a macro policy lever. The Federal Circuit has applied the doctrine to biotechnology cases in a way that would be inconceivable in other industries, such as software. The effect is to narrow the scope of biotechnology patents–or at least DNA patents–rather dramatically."); Alison E. Cantor, *Using the Written Description and Enablement Requirements to Limit Biotechnology Patents*, 14 HARV. J. LAW & TECH. 267, 313 (2000) ("If courts are strengthening the written description and enablement requirements in order to limit biotechnology patents, this fact raises concerns about creating special standards for particular areas of technology. If it is the courts that impose these standards, pioneering scientists in a new field will be unable to determine, when applying for patents, to what standard their patents will eventually be held when they are litigated.").

Moreover, a disproportionate number of patent cases where a dispute exists over the written description requirement under 35 U.S.C. § 112 involve medical technology patents. Indeed, an unscientific survey of the nine most recent precedential patent decisions of the Court of Appeals involving a written description requirement issue reveals seven of those cases pertaining to a medical technology invention. *See*

Tobinick v. Olmarker, No. 2013-1499, 2014 WL 2016141 (Fed. Cir. May 19, 2014) (pharmaceutical); *Alcon Research Ltd. v. Barr Labs. Inc.*, 745 F.3d 1180 (Fed. Cir. 2014) (pharmaceutical); *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725 (Fed. Cir. 2014) (pharmaceutical); *Takeda Pharm. Co. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359 (Fed. Cir. 2014) (pharmaceutical); *Synthes USA, LLC v. Spinal Kinetics, Inc.*, 734 F.3d 1332 (Fed. Cir. 2013) (medical device); *Trading Techs. Int'l, Inc. v. Open E Cry, LLC*, 728 F.3d 1309 (Fed. Cir. 2013) (software); *In re Bimeda Research & Dev. Ltd.*, 724 F.3d 1320 (Fed. Cir. 2013) (pharmaceutical); *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336 (Fed. Cir. 2013) (biotechnology).

Therefore, in practice, where a medical technology patent is involved, the claim construction often implicates the written description requirement of 35 U.S.C. § 112 in an effort to guide the interpretation according to the canon of construction to preserve validity if possible. Whether a claim satisfies the written description requirement is a question of fact. *See Alcon*, 745 F.3d at 1190. In this regard, the interplay with the invalidity issue of adequate written description will necessitate related factual findings for medical technology patent claim construction purposes.

2. A Greater Number of Findings of Fact During the Claim Construction of Medical Technology Patents Would Work a Disproportionate Burden on Medical Technology Innovation Under a Clear Error Review of a District Court's Claim Construction by the Court of Appeals.

Similar to the illustration *supra* with the written description requirement under 35 U.S.C. § 112, the other disclosure requirements of enablement and definiteness arise more often with medical technology patents than with those of other technologies. Both enablement and definiteness engender factual determinations. *See Green Edge Enters., LLC v. Rubber Mulch Etc.*, 620 F.3d 1287, 1299 (Fed. Cir. 2010) ("Definiteness, under 35 U.S.C. § 112, paragraph 2, and enablement, under paragraph 1, are both questions of law with underlying factual determinations.") (referring to the pre-America Invents Act statutory provisions, now 35 U.S.C. § 112(b) and 35 U.S.C. § 112(a), respectively). As with the invalidity issue of adequate written description, the interplay with the invalidity issues of enablement and definiteness will necessitate related factual findings for medical technology patent claim construction purposes. Therefore, to the extent this Court creates a new, clear error standard for appellate review of claim construction, medical technology patents would be disproportionately impacted.

II. Should This Court Eschew the Claim Construction Rubric This Court Set Forth in *Markman v. Westview Instruments, Inc.* in Favor of a Clear Error Review of a District Court's Claim Construction by the Court of Appeals, the Enforcement of Patent Rights Generally Would Be Burdened by Greater Inconsistency and Less Efficiency.

In *Markman*, this Court recognized the legislative mandate of the Court of Appeals, stating:

> Congress created the Court of Appeals for the Federal Circuit as an exclusive appellate court for patent cases observing that increased uniformity would "strengthen the United States patent system in such a way as to foster technological growth and industrial innovation"

Markman, 517 U.S. at 390. (citing H.R. REP No. 97-312, at 20-23 (1981)) (internal citations omitted). The reasoning supporting this Court's decision then to hold that claim construction is better decided by the judge than the jury applies with equal force almost two decades later. A change to require deference by the Court of Appeals to factual findings of the district court in claim construction belies this special legislative status. Moreover, the reason for change is unclear whereas the cost of such a change is certain. For the reasons set forth *supra*, this cost would be borne by medical technology patent holders disproportionately.

A. In Decades of Practice, the Court of Appeals *De Novo* Review of a District Court's Claim Construction Has Honored the Guidance That a District Court's Factual Findings Offer While Enabling the Federal Circuit's Expertise with Patent Claims to Benefit the Result.

In his concurring opinion in *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc), Circuit Judge William C. Bryson stated:

> While I join the opinion of the court without reservation, I think it important to note that our adoption of the rule that claim construction is an issue of law does not mean that we intend to disregard the work done by district courts in claim construction or that we will give no weight to a district court's conclusion as to claim construction, no matter how the court may have reached that conclusion. Simply because a particular issue is denominated a question of law does not mean that the reviewing court will attach no weight to the conclusion reached by the tribunal it reviews.

Id. at 1463. This sentiment captures the practical reality of claim construction *de novo* review by the Court of Appeals, which addresses the concern that the district courts' guidance is ignored. Furthermore, a change to a clear error standard of review will place a greater burden on district court judges in patent cases.

B. Any Shift Away From the Court of Appeals *De Novo* Review of a District Court's Claim Construction Will Unduly Elevate Expert Testimony and Result in Lengthier and Costlier District Court Proceedings in Patent Cases Generally.

In *Markman*, this Court noted that its "own experience with document construction leaves us doubtful that trial courts will run into many cases" "in which a simple credibility judgment would suffice to choose between experts whose testimony was equally consistent with a patent's internal logic." *Markman*, 517 U.S. at 389. A new, clear error standard for appellate review of claim construction, however, would increase the chances of this scenario. Under a more deferential standard of review, parties would be encouraged as a strategic consideration to rely more heavily on expert testimony before the district courts given the enhanced likelihood that any resulting factual findings will be upheld on appeal. Furthermore, the district courts will be required to provide more specific findings of fact to create a record amenable to review pursuant to FED. R. CIV. P. 52(a). The unfavorable result of such a change would be lengthier and costlier district court proceedings in patent cases generally.

CONCLUSION

For the foregoing reasons, *Amicus Curiae* respectfully submits that a departure from the claim construction rubric this Court set forth in *Markman v. Westview Instruments, Inc.* is unnecessary and would be detrimental, placing a disproportionate

burden on medical technology patents and raising the prospect that the development of critical lifesaving medical technology will be impeded. This Court should uphold plenary Court of Appeals review of claim construction, including any supporting factual findings.

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AMICUS CURIAE BRIEF

No. 13-854

In the

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,

PETITIONERS,

v.

SANDOZ, INC., ET AL.,

RESPONDENTS.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF GOOGLE INC., DELL INC., HEWLETT-PACKARD CO., SALESFORCE.COM, INC., TWITTER, INC., YAHOO! INC., ACUSHNET COMPANY, EBAY INC., KASPERSKY LAB, INC., LIMELIGHT NETWORKS, INC., NEWEGG INC., QVC, INC., SAS INSTITUTE INC., AND XILINX, INC. AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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INTEREST OF *AMICI CURIAE*[1]

Amici are high-technology and service companies that have driven innovation in a variety of fields, including: online search, advertising, commerce, collaboration, and social networking; electronics and computer hardware; open source software; and web hosting. Their products and services are used by everyday citizens, hundreds of Fortune 500 companies, the United States government, and other businesses and enterprises of all sizes. Having collectively invested hundreds of millions of dollars in research and innovation, *amici* own patent portfolios reflecting those efforts. They have also had to defend themselves against unprecedented levels of patent litigation, including meritless cases involving vague patents that offend the notice function of our patent system, chill future innovation, and divert capital away from research, products, and services that, unlike such patents, advance innovation and the public good. *Amici*'s considerable experience with patent litigation in general, and construction of patent claims in particular, gives them an experienced perspective on the question presented.

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[1] All parties have consented to the filing of this brief. No counsel for any party authored this brief in whole or in part, and no person or entity, other than *amici* or their counsel, made a monetary contribution intended to fund the preparation or submission of this brief.

INTRODUCTION AND SUMMARY OF ARGUMENT

This *amicus* brief focuses on three points. First, the court of appeals faithfully followed this Court's precedent holding that claim construction is "purely legal." *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996). Indeed, the *en banc* Federal Circuit has twice read *Markman* to mean exactly what it says. And legal questions are, of course, subject to *de novo* review. This Court should not pull the rug out from under the Federal Circuit's reliance on this Court's precedent.

Second, petitioners' attempt to evade that precedent is nothing short of radical. As this Court held just last Term, patents must provide the public with clear notice of their meaning, so the public can determine the boundaries of a patentee's exclusive property right with reasonable certainty. *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2130 (2014). According to petitioners, however, claim construction should turn on a battle of paid experts and other extrinsic "evidence" found nowhere in the public record of a patent application. That position would revolutionize claim construction itself (not just appellate review) and defeat the public-notice function of patent documents.

Purported fact findings based in whole or in part on expert testimony or other extrinsic evidence are either irrelevant to claim construction (such as a witness's credibility) or are properly viewed as legal rather than factual (such as a term's plain and ordinary meaning). Moreover, if a claim-construction dispute ultimately did boil down to a battle of experts

on a genuinely factual dispute, the claim would be invalid because its meaning would not be clear, as required by the definiteness requirement of 35 U.S.C. § 112.

Third, policy considerations strongly support treating claim construction as a question of law. Deferential review would undermine the important public-notice function of patents by empowering individual district judges to go their own ways on claim construction, and thereby promote the very forum shopping that Congress sought to eliminate by creating the Federal Circuit. Treating some aspects of claim construction as legal and others as factual would also skew claim-construction analysis by incentivizing district courts to rely more on so-called extrinsic evidence (which petitioners argue is factual), and less on what the patent documents actually say, in hopes of securing greater deference.

Classifying claim construction as being at least partly factual would also make patent litigation even more costly than it already is by discouraging courts from resolving claim construction disputes at the outset. Early claim construction is essential to enable parties to file summary judgment motions, or to engage in informed settlement discussions, before they have to incur potentially unnecessary discovery and other pre-trial costs. Those costs have become so exorbitant that many defendants settle even meritless cases solely to avoid them. For all of these reasons, deferential claim-construction review would only aggravate the uncertainty and expense that currently plague our patent system.

ARGUMENT

Petitioners' paean to Federal Rule of Civil Procedure 52(a) is irrelevant. *See, e.g.*, Pet. Br. i. Although that rule requires appellate courts to defer to factual findings, the standard of review for legal questions is, of course, *de novo*. *Cooper Indus., Inc. v. Leatherman Tool Grp., Inc.*, 532 U.S. 424, 436 (2001). And Rule 52(a) "does not furnish particular guidance with respect to distinguishing law from fact." *Pullman-Standard v. Swint*, 456 U.S. 273, 288 (1982). Courts must therefore "look outside the Rule to decide if a question is properly characterized as one of fact." *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1290 (Fed. Cir. 2014) (en banc); *see also, e.g., United States v. Gen. Motors Corp.*, 384 U.S. 127, 141 n.16 (1966) (interpretation of statute "is not to be shielded by the 'clearly erroneous' test embodied in Rule 52"). Claim construction is not.

I. THIS COURT HAS CORRECTLY HELD THAT CLAIM CONSTRUCTION IS A "PURELY LEGAL" ISSUE.

In *Markman*, the Federal Circuit held that courts should decide claim-construction issues and that "[b]ecause claim construction is a matter of law, the construction given the claims is reviewed *de novo* on appeal." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc). This Court granted review, expressly considered "whether the interpretation of a so-called patent claim is a *matter of law* reserved entirely for the court," and unanimously affirmed, holding that claim construction is "purely legal." *Markman*, 517 U.S. at

372, 391 (emphasis added). The Court explained that, for over a century, courts and scholars had declared claim construction to be a question of law. *See id.* at 385-88; *see also id.* at 384.

In support, this Court relied on authorities that cited plenary, *de novo* appellate review as a benefit of that approach. *Id.* at 388-89. As one of those authorities explained, a trial court's "decision as to the nature of the patented invention becomes reviewable to the same extent as any other legal question" precisely because claim construction is a question of law. 2 William C. Robinson, Law of Patents for Useful Inventions § 733, at 484 (1890); *see also Parker v. Hulme*, 18 F. Cas. 1138 (C.C.E.D. Pa. 1849) (No. 10,740).

Moreover, this Court's reasoning "necessarily implies de novo review." David Krinsky, *The Supreme Court, Stare Decisis, and the Role of Appellate Deference in Patent Claim Construction Appeals*, 66 Md. L. Rev. 194, 219 (2006). Highlighting the Federal Circuit's "exclusive" appellate jurisdiction for patent cases, the Court stressed "the importance of uniformity in the treatment of a given patent." *Markman*, 517 U.S. at 390. That uniformity comes from *de novo* appellate review; otherwise, courts in nearly 100 judicial districts could adopt different constructions so long as each construction was not clearly erroneous on the record of the particular case. And "[i]n th[at] increasingly frequent situation," "differing district court rulings on close questions of claim construction could well warrant affirmance on deferential review." *Lighting Ballast*, 744 F.3d at 1286.

The Court removed any doubt by emphasizing that "treating interpretive issues as *purely legal* will promote" uniformity "through the application of *stare decisis*." *Markman*, 517 U.S.at 391 (emphasis added). *Stare decisis* "commands judicial respect for a court's earlier decisions and the rules of *law* they embody," not its findings of *fact*. *Randall v. Sorrell*, 548 U.S. 230, 243 (2006) (plurality opinion) (emphasis added); *accord* 18 James W Moore et al., Moore's Federal Practice § 134.01 (3d ed. 2014); *Avenues in Leather, Inc. v. United States*, 423 F.3d 1326, 1331 (Fed. Cir. 2005). Thus, differing fact findings in separate cases do not implicate *stare decisis*, even if the ultimate issue (such as a patent's validity) is the same in both cases. *See Mendenhall v. Cedarapids, Inc.*, 5 F.3d 1557, 1570 (Fed. Cir. 1993); *Avenues in Leather*, 423 F.3d at 1331; *Stevenson v. Sears, Roebuck & Co.*, 713 F.2d 705, 711 (Fed. Cir. 1983). The *stare decisis* effect of claim constructions therefore confirms their purely legal nature.

Petitioners rely on the Court's description of claim construction as a "mongrel practice" with "evidentiary underpinnings." Pet. Br. 38-40 (quoting *Markman*, 517 U.S. at 378, 390). As the *en banc* Federal Circuit explained, however, those "prefatory comments" show only that the Court understood and considered the practical realities of claim construction; they do not change the Court's conclusion that it is best viewed as purely legal. *Cybor Corp. v. FAS Techs., Inc*, 138 F.3d 1448, 1455 (Fed. Cir. 1998) (en banc). Indeed, this Court expressly determined that, even when district courts receive and evaluate expert testimony, claim

construction remains on the law side of "'the fact/law distinction,'" in part because a court's consideration of such evidence "will be subsumed within the necessarily sophisticated analysis of the whole document." *Markman*, 517 U.S. at 388, 389 (quoting *Miller v. Fenton*, 474 U.S. 104, 114 (1985)). As explained below, that conclusion is correct and consistent with the standard of review applied to other "mongrel" questions in different areas of the law where courts consider questions from the perspective of a reasonable person with a certain background or experience. *See* pp. 8-9, *infra*. In context, therefore, petitioners' favorite passage in *Markman* shows only that there is nothing new here that would warrant reconsidering this Court's conclusion.

II. PROPER CLAIM CONSTRUCTION IS PURELY LEGAL.

This Court's precedents are correct: construction of patent documents is legal, not factual.

A. The Construction Of Written Instruments Is Generally A Question Of Law Subject To *De Novo* Review.

As this Court recognized in *Markman*, construction "of written instruments in patent litigation" should be no different "than in other cases implicating the meaning of documentary terms." 517 U.S. at 381-82; *see also id.* at 382-83; *Merrill v. Yeomans*, 94 U.S. (4 Otto) 568, 571 (1877). Indeed, the same general principles of law that apply in other contexts typically apply in patent cases as well. *See, e.g., MedImmune, Inc. v. Genentech, Inc.*, 549 U.S.

118, 128-29 (2007); *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 390 (2006); *Dickinson v. Zurko*, 527 U.S. 150, 165 (1999).

"[I]nterpreting a set of legal words" is "purely legal." *Buford v. United States*, 532 U.S. 59, 65 (2001). Statutory interpretation, for example, is always a question of law, even when it depends on a court's assessment of the ordinary meaning of a term at the time Congress enacted the statute. *McDermott Int'l, Inc. v. Wilander*, 498 U.S. 337, 356 (1991); *Slattery v. Roth*, 710 F.3d 1336, 1342 (Fed. Cir. 2013). Likewise, determining the plain meaning of a written contract based on the contract and a term's ordinary meaning is a pure question of law, subject to *de novo* review. *Firestone Tire & Rubber Co. v. Bruch*, 489 U.S. 101, 113 (1989); *Thatcher v. Kohl's Dep't Stores, Inc.*, 397 F.3d 1370, 1374 (Fed. Cir. 2005) (citing *South v. Rowe*, 759 F.2d 610, 613 (7th Cir. 1985)). So too for other written documents such as deeds, wills, and natural-resource leases. *See, e.g.*, *Maritimes & Ne. Pipeline, LLC v. Echo Easement Corridor, LLC*, 604 F.3d 44, 47 (1st Cir. 2010); *Terran v. Kaplan*, 109 F.3d 1428, 1432 (9th Cir. 1997); *Smoot v. Boise Cascade Corp.*, 942 F.2d 1408, 1411 (9th Cir. 1991); *Reese Exploration, Inc. v. Williams Natural Gas Co.*, 983 F.2d 1514, 1518 (10th Cir. 1993).

Patents are no exception to that general rule. Because a "patent is a fully integrated written instrument," *Markman*, 52 F.3d at 978, 985, "an analysis of the intrinsic evidence alone will resolve" most claim construction disputes. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir.

1996). That intrinsic evidence consists of the patent's specification, which includes claims and a written description of the claimed invention, as well as the patent's prosecution history, which is documented in the files of the Patent and Trademark Office. *See id.* at 1582. That public record of the patent prosecution shows how the applicant chose to describe the metes and bounds of the invention, and "the public is entitled to rely" on it. *Id.* at 1583.

Similar to statutory construction, therefore, claim construction turns on a term's ordinary meaning and the context provided by the patent documents as a whole. *See, e.g.*, *Markman*, 52 F.3d at 987 (analogizing claim construction to statutory construction). Simply put, "analyz[ing] *legal* documents (the patent and the prosecution history) to determine the *legal* significance of the words chosen by the patentee as well as *legal* significance of the public record in the patent office" is a legal inquiry. Steven C. Cherny et al., *2004 Patent Law Decisions of the Federal Circuit*, 54 Am. U. L. Rev. 941, 1049 (2005) (emphases added).

B. Proper Consideration Of Extrinsic Evidence Does Not Affect The Legal Nature Of Claim Construction.

Petitioners' contention that claim construction "often" turns on facts as opposed to the patent documents (Pet. Br. 25) is radical—not just as to the standard of appellate review, but as to the even more important question of how courts should construe claims in the first place. In an attempt to make claim construction factual, petitioners would subordinate the objective, intrinsic record to extrinsic

evidence, such as the testimony of hired experts. That would severely undermine the public-notice function of claims and this Court's recent *Nautilus* decision.

Under proper claim-construction principles, there are but two categories of potentially relevant extrinsic evidence: (i) dictionaries, treatises, and other reference materials that may demonstrate a word's plain and ordinary meaning to a person skilled in the art at the time a patent application was filed; and (ii) expert testimony that is limited to an elucidation of the background and perspective of such a person. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) (en banc). Assesssment of a term's ordinary meaning is a legal, not factual, inquiry. And expert testimony plays only the limited role of assisting the court in understanding the background and perspective of a person skilled in the art; construing the claims from that perspective remains a legal undertaking. Because truly factual questions (such as witness credibility) are not dispositive of proper claim constructions, they have no bearing on the standard of appellate review. Indeed, if a claim term's meaning depended on the resolution of a credibility determination, the term's meaning would not be reasonably clear—and the claim would be indefinite and thus invalid.

1. Patents' public-notice function confines extrinsic evidence to a very limited role in claim construction.

A party's decision to proffer extrinsic evidence alters neither the patent's meaning nor the standard of appellate review. Petitioners argue that

construction of a contract may depend on extrinsic evidence and that consideration of such evidence in contract cases is factual. *See* Pet. Br. 16. Contracts are, however, private agreements that affect only the rights of the contracting parties and their privies. For that reason, courts look to the "subjective intent of the parties when they entered into the agreement." *Markman*, 52 F.3d at 985; *see also Thatcher*, 397 F.3d at 1374.

In contrast, a patent "establishes a property right that applies throughout the nation." *Lighting Ballast*, 744 F.3d at 1285-86. Like statutes, patents are "public instruments [that] may create liability in third persons." *Markman*, 52 F.3d at 987. For that reason, extrinsic evidence of a patent applicant's subjective intent is irrelevant; by "review[ing] the public record,"a member of the public should be able to determine a claim's scope and adjust its behavior appropriately. *Vitronics*, 90 F.3d at 1583. "Allowing the public record to be altered or changed by extrinsic evidence introduced at trial, such as expert testimony," would undermine the public-notice function of claims. *Id.*

Indeed, extrinsic evidence is "less reliable" than the intrinsic, public record and is "unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Phillips*, 415 F.3d at 1318, 1319. Among other things, extrinsic evidence "is not part of the patent" and may suffer hindsight "bias." *Id.* at 1318. "[E]ach party will naturally choose the pieces of extrinsic evidence most favorable to its cause"—leading to the very real danger that courts will use

the evidence "to change the meaning of claims" and "thereby undermin[e] the public notice function of patents." *Id.* at 1318-19. Under correct claim construction principles, therefore, courts must focus on the intrinsic record.

2. A term's ordinary meaning is not a factual question.

Petitioners argue that, although claim construction is ultimately a question of law, determining a term's plain and ordinary meaning is a subsidiary question of fact. That position shows only how far they must stretch to try to describe proper claim construction as factual.

Courts may consider, in addition to a patent's intrinsic record, "dictionaries and treatises" that "collect the accepted meanings of terms used in various fields of science and technology." *Id.* at 1318. But consulting such written texts is not fact-finding because "dictionaries are admitted, not as evidence, but only as aids to the memory and understanding of the court." *Nix v. Hedden*, 149 U.S. 304, 306-07 (1893). Indeed, statutory construction is a purely legal undertaking subject to *de novo* review even though courts routinely consult dictionaries to determine a word's meaning at the time Congress enacted the statute (sometimes decades earlier). *See* p. 8, *supra*. Just as "[r]eference to technical understanding and usage at the time of enactment does not convert statutory interpretation from law to fact," it does not convert claim construction into a factual inquiry, either. *Lighting Ballast*, 744 F.3d at 1284; *see also id.* at 1284-85 (citing *Sandifer v. U.S. Steel Corp.*, 134 S. Ct. 870 (2014); *Comm'r v.*

Soliman, 506 U.S. 168 (1993); and *Chapman v. United States*, 500 U.S. 453 (1991)).

Even in the rare circumstance in which dictionaries squarely conflict, such that they do *not* reveal a single plain and ordinary meaning for a claim term, a court does not "find facts" by choosing one dictionary over the other. If dictionaries conflicted, the question would not be which dictionary definition was best in some abstract sense; it would be which proposed definition fit best in the context of the patent and prosecution history. *See Vitronics*, 90 F.3d at 1583. Especially considering the need to determine a word's meaning in the context of a patent's intrinsic record, treating part of the holistic interpretive analysis as legal and part as factual would make little sense.

3. Construing claims from the perspective of a person skilled in the art does not make claim construction factual.

Petitioners also contend that, because claims must be construed from the perspective of a person of "ordinary skill in the art" at the time of the patent application, claim construction depends on factual, expert testimony about the background and perspective of such a person. Pet. Br. 26-30. Under that theory, claim construction would typically if not always be a "battle of [the] experts" (Pet. Br. 37), as petitioners acknowledge, and the public-notice function of claims could be defeated by whatever a paid expert testified to in a particular case.

That has never been the law. When a district court lacks familiarity with the relevant scientific

discipline, it has discretion (though not an obligation) to consider "background" testimony regarding the knowledge and experience of a person skilled in the art, as well as testimony about "how an invention works." *Phillips*, 415 F.3d at 1318. But that testimony only provides *context* for claim construction by helping a court understand and adopt the perspective of a person skilled in the art. *See Markman*, 517 U.S. at 388; *Markman*, 52 F.3d at 981.

The actual construction of a claim is then a question of law for a court. As this Court explained, courts may receive "the testimony of witnesses" for contextual purposes, but "in the actual interpretation of the patent the court proceeds upon its own responsibility, as an arbiter of the law, giving to the patent its true and final character and force," *Markman*, 517 U.S. at 388 (quoting 2 Robinson, Law of Patents § 732, at 481-83). *See also* Albert H. Walker, Text-book of the Patent Laws of the United States of America § 189, at 146-47 (2d ed. 1889); *Lighting Ballast*, 744 F.3d at 1284. Indeed, "professors or mechanics cannot be received to prove to the court or jury what is the proper or legal construction of any instrument of writing." *Winans v. New York & Erie R.R. Co.*, 62 U.S. (21 How.) 88, 101 (1859).

As a result, acquiring familiarity with the background and context through expert testimony is not akin to finding facts, much less facts that are dispositive of a proper claim construction. After adopting the perspective of a person skilled in the art, the court itself must construe the claims "based

upon the patent and prosecution history." *Markman*, 52 F.3d at 981. And because claim construction focuses on the objective meaning of the patent documents, courts that entertain expert testimony or other extrinsic evidence are "*not* crediting certain evidence over other evidence or making factual evidentiary findings." *Id.*; *see also Mitchell v. Tilghman*, 86 U.S. (19 Wall.) 287, 379-90 (1874) (searching review of claim construction based on extrinsic evidence), *overruled in part on other grounds*, *Tilghman v. Proctor*, 102 U.S. (12 Otto.) 707, 708 (1880). Courts must test conflicting experts' testimonies, just like any conflicting dictionary definitions, against the intrinsic evidence—not against each other in a credibility battle.

As this Court summed up the point, "any credibility determinations will be subsumed within the necessarily sophisticated analysis of the whole document, required by the standard construction rule that a term can be defined only in a way that comports with the instrument as a whole." *Markman*, 517 U.S. at 389. In other words, if a court ultimately agrees with one expert and disagrees with another, the reason should be that the first expert's testimony is more consistent with the intrinsic record, and thus more persuasive. The question is not whether one witness was lying and another was not.

The expert testimony serves only to inform the court's legal analysis, and a question does not become factual simply because an expert testified to it. *Cf. KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 426-27 (2007) (rejecting attempt to use expert testimony to

create dispute of fact on issue of law). "An expert's opinion on the ultimate legal conclusion is neither required nor indeed 'evidence' at all." *Nutrition 21 v. United States*, 930 F.2d 867, 871 n.2 (Fed. Cir. 1991).

Significantly, appellate courts conduct *de novo* review of analogous questions in other areas of law where a court must assume the perspective of a reasonable person with a particular background or experience. When a district court determines whether the facts "amount[ed] to reasonable suspicion or to probable cause" when "viewed from the standpoint of an objectively reasonable police officer," for example, appellate review is *de novo*. *Ornelas v. United States*, 517 U.S. 690, 696 (1996). Courts likewise review *de novo* the "amphibian" question whether a confession was voluntary. *Miller*, 474 U.S. at 116.

It also bears emphasis that *amici*, who have collectively litigated hundreds of patent cases, are aware of no case in which a dispute over the perspective of a person skilled in the art actually mattered to claim construction. That perspective can be important for other patent-law issues, such as whether a claimed invention would have been obvious to such a person. *See KSR Int'l Co.*, 550 U.S. 398. But claim construction, like statutory construction, is a fundamentally legal analysis of a term's ordinary meaning and the context provided by the intrinsic evidence. That analysis is what it is. Treating all claim construction as factual because it is viewed from the perspective of a person skilled in the art would therefore convert a fundamentally legal

question into a factual one based on a wholly contrived portrayal of the claim-construction process.

4. Reliance on conflicting extrinsic evidence never drives a proper claim construction, though it may show that the claim is indefinite.

While extrinsic evidence generally has limited value, *conflicting* extrinsic evidence has particularly little value to proper claim construction. Any conflicts in the extrinsic evidence would show at most that such evidence was not sufficiently clear to shed much light on the meaning of the intrinsic evidence. *See, e.g.*, *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1368 (Fed. Cir. 2002); *Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1372-73 (Fed. Cir. 1998); *cf. Mitchell*, 86 U.S. (19 Wall.) at 417 (experts "differ so widely in opinion that their testimony affords the court but little aid"). Because disputes over genuinely factual issues are not dispositive of proper claim constructions, they are not relevant to the standard of appellate review.

Indeed, while some members of the Federal Circuit have discussed the possibility of an "atypical case" in which "the district court found it necessary to resolve conflicting expert evidence," *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 469 F.3d 1039, 1045 (Fed. Cir. 2006) (en banc) (concurrence of Gajarsa, Linn, and Dyk, JJ.); *see also Markman*, 517 U.S. at 389), such a case has proven to be "ever-elusive" precisely because claim constructions should not depend on such battles of the experts. *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 659 F.3d 1369, 1373 (Fed. Cir. 2011) (en banc) (Moore, J.,

dissenting). *Amici* are aware of no case in which such a resolution was necessary.

This is certainly not such a case. As explained in the briefs of respondents and some other *amici*, petitioners proffered expert testimony to (i) contradict what the patent documents actually say on some topics and (ii) try to make up for those documents' failure to provide clear notice of the claim scope, as required by Section 112's definiteness requirement. As those briefs further explain, proper claim construction is not open to such manipulation. Testimony is relevant only to the extent that it helps a reader understand the intrinsic evidence, not to the extent that it tries to replace the patents' disclosures. Similarly, Section 112 requires that the patent documents' meaning actually be clear, not that an expert can later testify to his purported understanding. Indeed, any competent attorney can find an expert to give content to gaps left open—often deliberately—by the applicant. *Cf. Nautilus*, 134 S. Ct. at 2129 ("patent applicants face powerful incentives to inject ambiguity into their claims").

In *Markman*, this Court speculated that "in theory there could be a case in which a simple credibility judgment would suffice to choose between experts whose testimony was equally consistent with a patent's internal logic." 517 U.S. at 389. Even if such a theoretical, knife's-edge case were to come along, the patent claim would be indefinite and thus invalid. If a patent's "internal logic" were reasonably interpreted in diametrically opposite ways, its meaning would not be reasonably clear, as required

by Section 112. *See Nautilus*, 134 S. Ct. at 2129; *Markman*, 52 F.3d at 986.

Similarly, a court's perceived need to make a credibility determination in order to resolve a battle of the experts would necessarily mean that the claim's meaning was not "clear" and "exact." 35 U.S.C. § 112(a). As discussed above, the public deserves "reasonabl[y] certain[]" notice of claim scope—not claims that are so ambiguous that their meaning boils down to a credibility determination between two paid experts in litigation brought years after the patent issued. *Nautilus*, 134 S. Ct. at 2129; *see also United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 236 (1942) (claims must be "reasonably clearcut").

III. PRACTICAL CONSIDERATIONS SUPPORT *DE NOVO* APPELLATE REVIEW OF CLAIM CONSTRUCTIONS.

Our patent system already faces serious problems with vague claims, unpredictable and inconsistent claim constructions, and costly litigation. Deferring to district-court claim constructions would only make those problems worse.

A. Deference Under The Clear-Error Standard Would Increase Uncertainty And Undermine The Public-Notice Function Of Claims.

Petitioners contend that deferential review would decrease uncertainty within any given case by making reversal on appeal less likely. But there is little reason to believe that fewer reversals on this issue would be a positive development. Even if it

were, accomplishing that result through a deferential standard of review would actually increase the overall level of uncertainty associated with unclear claims.

1. Although petitioners argue that the Federal Circuit's reversal rate for claim constructions is too high (Pet. Br. 49, 53), that rate has decreased in the past decade and is overstated due to selection bias resulting from the fact that only the hardest cases are appealed. *See* J. Jonas Anderson & Peter S. Menell, *Informal Deference: A Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 Nw. U. L. Rev. 1, 1 (2014); Richard S. Gruner, *How High Is Too High?: Reflections on the Sources and Meaning of Claim Construction Reversal Rates at the Federal Circuit*, 43 Loy. L.A. L. Rev. 981, 981 (2010). In any event, appellate courts sit for the very purpose of reviewing district court decisions and there is no reason to believe that the reversal rate on this issue is inappropriate.

2. Even if a lower reversal rate were preferable, the solution would not be to reduce it arbitrarily by reversing only the most clearly wrong constructions while allowing other wrong constructions to stand. That would make no more sense than trying to cure a disease by diagnosing only the most extreme cases, or trying to repair water damage from a leaky roof by repainting the ceiling without plugging the leak. Instead of using a deferential standard of review to essentially conceal the seriousness of the underlying problems, this Court should address them. Claims no longer serve the public-notice function they are supposed to, in part because they are often drafted in

deliberately ambiguous terms. As this Court has recognized, claims' ambiguity invites abuse by patentees and increases litigation costs and uncertainties. *Nautilus*, 134 S. Ct. at 2129.

And the Federal Circuit has aggravated the uncertainty through inconsistent application of "the tools available for claim construction." Kimberly A. Moore, Markman *Eight Years Later: Is Claim Construction More Predictable?*, 9 Lewis & Clark L. Rev. 231, 247 (2005). The Federal Circuit has announced two axioms of claim construction: courts must interpret claims in light of the patent's specification, and they must not import limitations into the claims from the specification. *See Phillips*, 415 F.3d at 1315, 1323. Panels have often divided over how to reconcile these statements, essentially breaking down into two camps. Some judges determine a term's purported plain and ordinary meaning in the abstract, before looking to the context provided by the patent's specification, and hold that the abstract meaning controls unless the patent *clearly* contradicts it. *E.g.*, *nCube Corp. v. Seachange Int'l, Inc.*, 436 F.3d 1317 (Fed. Cir. 2006). Other judges recognize that context plays a far more important role in proper construction, such that claim terms should be construed in keeping with the patent's specification, especially its description of the claimed invention. *E.g.*, *Digital-Vending Servs. Int'l, LLC v. Univ. of Phx., Inc.*, 672 F.3d 1270, 1276 (Fed. Cir. 2012).

The second of those approaches is the correct one. This Court has long held that "claims are to be construed in the light of the specifications and both

are to be read with a view to ascertaining the invention." *United States v. Adams*, 383 U.S. 39, 48-49 (1966). It is improper to ignore the specification in favor of a "plain meaning" analysis divorced from the context of the patent. Indeed, this Court has repeatedly emphasized that whether a term's meaning is clear *depends* on the context in which it is used. *See, e.g., FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132-33 (2000) (construing statutes).

Federal Circuit judges and commentators have, nonetheless, repeatedly acknowledged that court's fundamental divide on proper claim-construction methodology. *See* Thomas W Krause & Heather F Auyang, *What Reversals and Close Cases Reveal About Claim Construction: The Sequel*, 13 J. Marshall Rev. Intell. Prop. L. 525, 537-50 (2014).

3. The application of such improper and inconsistent claim-construction methodology, along with vaguely drafted claims, are the root causes of the uncertainty plaguing this area. Deference would not resolve those causes of uncertainty; it would likely make them worse for at least two reasons.

First, some courts currently prefer to hear expert evidence while others eschew the practice. Neither approach would necessarily be unreasonable or clearly erroneous on a case-by-case basis—meaning that the standard of review could depend on the district court's chosen *methodology* for claim construction, and in practice the Federal Circuit would have to defer as much to the district court's methodology as to its findings. As such, the meaning of a patent claim could depend more on the court in

which a case was filed than on the intrinsic or extrinsic evidence. Plaintiffs would be tempted to engage "in the same kind of forum-shopping that existed before the Federal Circuit's creation." Lauren Maida, *Patent Claim Construction: It's Not a Pure Matter of Law, So Why Isn't the Federal Circuit Giving the District Courts the Deference They Deserve?*, 30 Cardozo L. Rev. 1773, 1788 (2009).

Second, the one certainty is that, if a district court's consideration of extrinsic evidence were entitled to deference under the clear-error standard, extrinsic evidence would assume a greater role in claim construction. Litigants would have every reason to present extrinsic evidence so that, if they prevailed in the district court, they could rely on deference on appeal. If petitioners carried the day, plaintiffs would be incentivized to engage in "expert shopping," looking for an expert willing to testify about ambiguous patent claims according to the demands of the particular lawsuit.

District courts would also have a strong incentive to rely on expert testimony and other extrinsic evidence to secure deferential review. Under a clear-error standard, "reliance on extrinsic evidence can be an important way for trial courts to bolster the 'factual' nature of their findings and promote deferential review on appeal." Peter S. Menell et al., *Patent Claim Construction: A Modern Synthesis and Structured Framework*, 25 Berkeley Tech. L.J. 711, 727 (2010); *see also id.* at 814-15. Indeed, some commentators have proposed deference for the very purpose of increasing the use of extrinsic evidence—even to the point of arguing that district courts

should *first* look to extrinsic evidence and then determine if the intrinsic evidence is compatible with it. *See* Cherny et al., 54 Am. U. L. Rev. at 1049-50. As explained above, that backwards approach would badly undermine the public-notice function of patents.

B. Deference Under The Clear-Error Standard Would Increase The Overall Cost Of Litigation.

Petitioners observe that a deferential standard of review could reduce the cost of litigating *some* cases by reducing the number of cases in which the Federal Circuit reverses a claim construction, vacates the district court's judgment, and remands for further proceedings. Pet. Br. 49-53. But that would be a Pyrrhic victory for patent litigants. Classifying claim construction as being at least partly factual would encourage trial judges not to resolve claim constructions at the outset of a case, but instead to defer them for consideration with other factual issues after the close of discovery. *See* Maida, 30 Cardozo L. Rev. at 1794.

Delaying claim construction would impose a tremendous burden in the mine run of cases far in excess of cost savings realized in the much smaller number of cases in which deferential review caused the Federal Circuit to affirm a claim construction it believed to be wrong. Parties would have to serve expert reports and file summary judgment motions applying multiple possible understandings of the claims. If the district court withheld claim construction until after entertaining trial evidence, the parties may even have to present alternative

cases to the jury based on different claim interpretations—resulting inevitably in jury confusion. And all would be for naught if the court disagreed with both parties' constructions and crafted its own.

In contrast, early claim construction enables litigants to file potentially dispositive motions, and conduct informed settlement discussions, before incurring further litigation costs. In a survey of over 500 practitioners, the vast majority identified early claim construction as an effective method of battling rising patent litigation costs. Colleen V. Chien et al., *Santa Clara Best Practices in Patent Litigation Survey*, at i, http://ssrn.com/abstract=2321363 (forthcoming 42 AIPLA Q.J. _, 2014). Efficient resolution of meritorious defenses, and summary judgments for plaintiffs and defendants alike, are especially important because patent suits are extraordinarily expensive to litigate and subject to material uncertainty. Dep't of Commerce, *Patent Reform: Unleashing Innovation, Promoting Economic Growth & Producing High-Paying Jobs*, at 5-6 (Apr. 13, 2010), http://www.commerce.gov/sites/default/files/documents/migrated/Patent_Reform-paper.pdf. Patent litigation costs have soared to an average of $5 million in cases where plaintiffs seek more than $25 million in damages and $2.5 million for lesser damages demands. *See* AIPLA, Report of the Economic Survey 2011, at 35.

Avoiding infringement of patents by designing around them during product development, or negotiating a reasonable license before design decisions are finalized, is often infeasible due to

"notice failure": because broad, ambiguous claims are difficult to interpret and there are so many of them, "innovative firms are targeted in patent infringement suits through no fault of their own." James Besson & Michael J. Meurer, *The Direct Costs from NPE Disputes*, 99 Cornell L. Rev. 387, 393-94 (2014). "Especially for business methods and software, the patent system provides innovators who might be targeted with a patent suit with little information about the existence, ownership, or scope of relevant patent rights." *Id.* at 418; *see also* Christopher R. Leslie, *The Anticompetitive Effects of Unenforced Invalid Patents*, 91 Minn. L. Rev. 101, 113-29 (2006).

Such uncertainty plays into the hands of patent-assertion entities ("PAEs"). As the Federal Trade Commission found, PAEs obtain "overbroad, vague claims" they might assert against a broad range of activity, wait for others to do the hard work of developing applications—and then sue the real innovators. *See* Fed. Trade Comm'n, *The Evolving IP Marketplace*, at 8-9, 50-51, 60-61 (Mar. 2011), http://www.ftc.gov/os/2011/03/110307patentreport.pdf. One study found that PAE suits were associated with "*half a trillion dollars* of lost wealth to defendants from 1990 through 2010" (or roughly $25 billion per year). James Bessen et al., *Private and Social Costs of Patent Trolls*, 34 Regulation 26, 26 (Winter 2011-2012), http://object.cato.org/sites/cato.org/ files/serials /files/regulation/2012/5/v34n4-1.pdf (emphasis added). That trend has only continued since then; the most recent study estimated that the direct costs of PAE suits in 2011 totaled $29 billion. Besson & Meurer, 99 Cornell L. Rev. at 387.

Lawsuits brought by PAEs have quadrupled since 2005 and now account for a majority of patent litigation. *See* RPX Corp., *NPEs Have Broader Impact Than GAO Headlines* Suggest (Sept. 9, 2013), http://www.rpxcorp.com/2013/09/09/npes-have-broader-impact-than-gao-headlines-suggest-2/; RPX Corp., *Tracking PAE Activity* (Jan. 23, 2013), http://www.rpxcorp.com/2013/01/23/tracking-pae-activity-a-post-script-to-the-doj-review/.

Faced with this reality, most companies already pay substantial sums to settle meritless cases because their litigation expenses would exceed the plaintiff's settlement demand. *See, e.g.*, Brian J. Love *Why Patentable Subject Matter Matters for Software*, 81 Geo. Wash. L. Rev. Arguendo 1, 9–10 (2012), http://www.gwlr.org/wp-content/uploads/2012/09/Love_Arguendo_81_1.pdf. Discovery costs alone have become a powerful incentive for some patent plaintiffs to file strike suits for quick settlements. *See Eon-Net LP v. Flagstar Bancorp*, 653 F.3d 1314, 1327 (Fed. Cir. 2011).

By reiterating that claim construction is a question of law, this Court would encourage district courts to resolve that threshold legal issue early in a case, saving hundreds of millions of dollars in litigation costs, deterring nuisance suits, and conserving scarce judicial resources.

C. The Reviewing Court Can Best Provide Uniform Claim Constructions.

Of course, an "appellate court is just as capable as the district court at evaluating intrinsic evidence" by reading the patent documents. Timothy J. Malloy & Patrick V. Bradley, *Claim Construction: A Plea for*

Deference, 7 Sedona Conf. J. 191, 198 (2006); *see also* Cherny et al., 54 Am. U. L. Rev. at 1049. So too for dictionaries and other reference materials. *See* p. 12, *supra*. While district courts may benefit in some cases from hearing live expert testimony, the value of that testimony ultimately depends on its consistency with the intrinsic evidence—a determination appellate courts are well positioned to make. *See* p. 15, *supra*.

The main difference is that an appellate court may bring greater time, attention, and expertise to any given claim construction issue. Indeed, petitioners' contention that district courts have more time and resources for claim construction (Pet. Br. 50-51) is fanciful. District court procedures are uneven: "Some allocate multiple days to the hearing, while others determine claim construction on the papers." Menell et al., 25 Berkeley Tech L.J, at 818.

And no matter how conscientious a district judge might be, the judge is generally tasked with construing many more claim terms at an earlier point in the case, and with ruling on many other issues as well. In contrast, litigants typically raise far fewer issues on appeal, enabling the appellate court (and the appellate briefing) to focus on only the most important claim constructions. When a claim-construction (or any other) issue is "the focus of appellate review, it can be expected that the parties' briefs will be refined to bring to bear on the legal issues more information and more comprehensive analysis than was provided for the district judge." *Salve Regina Coll. v. Russell*, 499 U.S. 225, 232 (1991). In addition, because the Federal Circuit

reviews claim constructions by all of the district courts, it is "structurally suited to the collaborative juridical process that promotes decisional accuracy." *Id.*

In any event, the Federal Circuit is the only court that can discharge its mandate to provide national uniformity. *Markman*, 517 U.S. at 390, 391. Deferential review would require the appellate courts to affirm claim constructions supported by merely reasonable—*i.e.*, not clearly erroneous—rationales. When a patent is litigated in different jurisdictions, deference could easily result in the affirmance of opposing constructions, especially if the district courts relied on purported "credibility" determinations. Because patent claims demarcate property rights, however, they should have a "true and final character"—not meanings that turn on a plaintiff's choice of forum or on which expert testifies in a given case. *See* 2 Robinson, Law of Patents § 732, at 481-83; *Salve*, 499 U.S. at 234 (citing forum shopping concerns relevant to appellate standard of review). "[T]he stakes—in terms of impact on future cases and future conduct—are too great to entrust them finally to the judgment of the trier of fact." *Bose Corp. v. Consumers Union of U.S., Inc.*, 466 U.S. 485, 501 n.17 (1984).

That does not mean that reviewing courts should ignore a district court's reasoning. "[E]fficient and sensitive appellate" review "will naturally consider" the district court's analysis. *Salve*, 499 U.S. at 232. *De novo* review "does not mean that we intend to disregard the work done by district courts in claim construction or that we will give no weight to a

district court's conclusion as to claim construction, no matter how the court may have reached that conclusion." *Cybor*, 138 F.3d at 1463 (Bryson, J., concurring). In appropriate circumstances, such as when a district court has carefully considered a technically complex issue after hearing from witnesses, "it would be entirely appropriate—and consistent with our characterization of claim construction as a question of law—to factor into our legal analysis the district court's superior access to one of the pertinent tools of construction." *Id.*; *see also Miller*, 474 U.S. at 114.

Courts apply similar deference in other contexts. Even when an administrative agency's legal conclusion is not entitled to *Chevron* deference, for example, courts may defer informally. *See, e.g.*, *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944). The degree of deference turns on the administrative decision's "power to persuade," such as the amount of consideration the agency gave to the issue. *See id.* A reviewing court is free to treat claim construction similarly. *See* Lee Petherbridge, *Positive Examinati[illegible]*, 46 IDEA 173, 216 (2006) (calling for "Skidmore-like deference" for claim construction). That would make far more sense than clear-error review because informal deference could turn, for example, on whether a judge *actually* gave a claim construction careful consideration after hearing relevant testimony on technically complex matters.

CONCLUSION

For the foregoing reasons, the judgment of the court of appeals should be affirmed.

Respectfully submitted,

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August 18, 2014

AMICUS CURIAE BRIEF

No. 13-854

IN THE
SUPREME COURT OF THE UNITED STATES

TEVA PHARMACEUTICALS USA, INC.,
TEVA PHARMACEUTICAL INDUSTRIES, LTD.,
TEVA NEUROSCIENCE, INC., AND YEDA
RESEARCH AND DEVELOPMENT CO., LTD.,
Petitioners,

v.

SANDOZ INC.,
MOMENTA PHARMACEUTICALS INC.,
MYLAN PHARMACEUTICALS INC.,
MYLAN INC., AND NATCO PHARMA LTD.,
Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR *AMICUS CURIAE* HOUSTON INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF NEITHER PARTY

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June 20, 2014

QUESTION PRESENTED

Whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel explicitly did in this case), or only for clear error, as Federal Rule of Civil Procedure 52(a) requires?

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INTEREST OF *AMICUS CURIAE*

The Houston Intellectual Property Law Association ("HIPLA") is an association of over 400 lawyers and other professionals who predominately work in the Houston, Texas, area (see, generally, www.hipla.org). The practice of most of the HIPLA membership relates in substantial part to the field of intellectual property law. Founded in 1961, HIPLA is one of the largest associations of intellectual property practitioners in the United States.[1]

Consent to the filing of *amicus curiae* briefs in support of either party or of neither party was submitted to the Clerk by counsel for Respondent Mylan Pharmaceuticals, Inc., et al. Consent to the filing of HIPLA's *amicus curiae* brief in support of neither party was received from counsel of record for the Petitioners Teva Pharmaceuticals USA, Inc., et al., by letter dated June 10, 2014. And counsel for Sandoz, Inc., et al., consented to HIPLA's filing of its *amicus curiae* brief supporting neither party by letter dated June 13, 2014.

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[1] No counsel for a party in this case authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity other than HIPLA, its members, or its counsel paid for this brief.

HIPLA has no stake in the outcome of this litigation. But HIPLA is interested in promoting consistency in the development of the law affecting patents and other forms of intellectual property.

SUMMARY OF ARGUMENT

The interpretation of patent claims, like that of other legal instruments, is ultimately a question of law. But claim interpretation can also depend on the resolution of underlying factual issues. Claim interpretation, thus, presents a hybrid mix of factual and legal issues that are resolved by a district court in determining the meaning of disputed claim terms. Having already recognized that claim construction can be a "mongrel practice," this Court should now mandate a hybrid fact/law approach for appellate review of claim constructions.

Under a hybrid approach, fact findings made by a district court judge would be reviewed for clear error under Rule 52(a). Legal conclusions as to the meaning of claim terms under established claim construction precedent would continue to be reviewed *de novo*. This approach is consistent with this Court's decisions on obviousness and the Federal Circuit's decisions on enablement (two other areas of mixed law and fact). Policy concerns of litigation efficiency and proper allocation of

judicial resources with national uniformity in the treatment of patents is also satisfied by such a hybrid approach.

This Court has recognized that distinguishing between fact findings and legal conclusions can be difficult. But adopting a hybrid review standard will require these distinctions to be made, and HIPLA urges this Court to provide additional guidance that facilitates implementation of this standard. Particularly, this Court should clarify that claim meaning, even when considered from the perspective of a skilled artisan at the time of invention, is a question of law subject to *de novo* review.

ARGUMENT

I. A district court's fact findings during claim construction should not be overturned unless clearly erroneous.

In *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), this Court held that, as between a district court judge and a jury, the interpretation of claim terms falls within the exclusive province of the court. *Id.* at 376. Although this Court did not directly address in *Markman* the standard of review for claim construction, the Federal Circuit en banc held that a *de novo* standard is proper. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1451

(Fed. Cir. 1998) (en banc) ("[C]laim construction, as a purely legal issue, is subject to *de novo* review on appeal."); *accord Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 723 F.3d 1363, 1373 (Fed Cir. 2013) ("Claim construction is an issue of law that we review *de novo*."). The en banc Federal Circuit recently reconsidered and, applying *stare decisis*, affirmed its holding in *Cybor*, holding that claim construction is a purely legal issue subject to *de novo* review. *Lighting Ballast Control LLC v. Philips Electronics N. Am. Corp.*, 744 F.3d 1272, 1276–77 (Fed. Cir. 2014) (en banc).

But the Federal Circuit's holdings conflict with this Court's recognition that claim construction, in at least some instances, can raise issues of both fact and law. *See Markman*, 517 U.S. at 378 (describing claim construction following receipt of evidence as a "mongrel practice"). This Court has further suggested that claim construction can fall "somewhere between a pristine legal standard and a simple historical fact." *Id.* at 388 (quoting *Miller v. Fenton*, 474 U.S. 104, 114 (1985)).

Moreover, a careful reading of the *Markman* opinion indicates that this Court defers to the district judge for answering factual questions that are subsidiary to claim construction (e.g., "credibility judgments about the experts who testify in patent cases," 517 U.S. at 389). For example, this Court noted in *Markman* that:

> The decisionmaker vested with the task of construing the patent is in the better position to ascertain whether an expert's proposed definition fully comports with the specification and claims and so will preserve the patent's internal coherence. We accordingly think there is sufficient reason to treat construction of terms of art like many other responsibilities that we cede to a judge in the normal course of trial, notwithstanding its evidentiary underpinnings.

517 U.S. at 390.

As Professors Jonas Anderson and Peter Menell have detailed, the Federal Circuit appears not to have sufficiently considered that this Court in *Markman* is expressing its appreciation that claim construction rulings are analogous to other "rulings that a trial judge routinely resolves during the course of trial, which are not subject to *de novo* review." J. Jonas Anderson & Peter S. Menell, *Informal Deference: A Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 NW. U. L. REV. 1, 66 (2014). Professors Anderson and Menell maintain:

> Thus, the more plausible interpretation of the full passage is that the Supreme Court is inclined toward a deferential standard of review of claim construction determinations reflecting the inherently "mongrel"—mixed

> fact and law—character of claim construction.

Id.

Justifying its plenary *de novo* review standard in *Cybor*, the Federal Circuit characterized this Court's *Markman* opinion as providing "only prefatory comments demonstrating the Supreme Court's recognition that the determination of whether patent claim construction is a question of law or fact is not simple or clear cut." *Cybor*, 138 F.3d at 1455. While *Markman* does give various precedential and historical reasons for concluding that claim construction is a question of law, it does not mandate sacrificing a district court's fact findings at the altar of the Federal Circuit's plenary *de novo* review standard. *See Markman*, 517 U.S. at 384–88. Rather, the most natural reading of this Court's decision in *Markman* is that the process of construing a claim term may indeed depend on the resolution of underlying fact questions. To the extent that *Cybor* and *Lighting Ballast* hold otherwise, they should be overruled.

Another area of patent law having a similar mix of factual and legal questions is obviousness under 35 U.S.C. § 103. Although the ultimate conclusion of whether a claim is obvious is a question of law, this conclusion is founded upon underlying facts. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007); *Graham v. John Deere Co. of Kansas City*,

383 U.S. 1, 17–18 (1966). These underlying facts include the scope and content of the prior art, the differences between the prior art and claims at issue, the level of ordinary skill in the art, and any secondary considerations (e.g., commercial success, long-felt but unsolved needs, and failure of others). *KSR Int'l*, 550 U.S. at 427; *Graham*, 383 U.S. at 17.

Once these factual determinations are made, the district court then determines, as a matter of law, whether a claim at issue is obvious. And this Court long ago concluded that factual determinations underlying the obviousness inquiry are subject to Rule 52(a) and must be reviewed deferentially under the clear error standard. *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 811 (1986) ("the subsidiary determinations of the District Court, at the least, ought to be subject to the Rule.").

Dennison is consistent with this Court's other decisions indicating that Rule 52(a)'s clear error standard is broadly applicable to fact findings. *See* Eileen M. Herlihy, *Appellate Review of Patent Claim Construction: Should the Federal Circuit Be Its Own Lexicographer in Matters Related to the Seventh Amendment*, 15 MICH. TELECOMM. & TECH. L. REV. 469, 499 (2009) (noting the consistency of the decisions regarding the broad applicability of Rule 52(a) in *Dennison*, *Pullman-Standard v. Swint*, 456 U.S. 273 (1982), and *Bose Corp. v.*

Consumers Union of United States, Inc., 466 U.S. 485 (1984)).

In the context of enablement determinations, that is, whether a patent's specification provides enough detail to explain how the claims work to a person of ordinary skill in the relevant art, the Federal Circuit also applies a clear error analysis to a district court's fact findings. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1369–70 (Fed. Cir. 1999) ("Whether undue experimentation would have been required to make and use an invention, and thus whether a disclosure is enabling under 35 U.S.C. § 112, ¶ 1, is a question of law that we review *de novo*, based on underlying factual inquiries that we review for clear error. *See Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1354 (Fed. Cir. 1998) (citing *Wands*, 858 F.2d at 736–37)."); *see also ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) ("The district court's determination of the hypothetical person of ordinary skill in the relevant art is a finding of fact we review for clear error. *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966).")

Rule 52(a) should equally apply to appellate review of claim construction rulings. The factual underpinnings of claim construction orders should be reviewed deferentially and not overturned unless clearly erroneous.

Moreover, a rule for deferential review of fact findings is consistent with this Court's recent decision in *Highmark Inc. v. Allcare Health Mgmt. Sys., Inc.*, 572 U.S. ___ (2014). Although founded upon exceptional case determinations under 35 U.S.C. § 285, this Court in *Highmark* clearly stated:

> As in *Pierce* [*v. Underwood*, 487 U.S. 552 (1988)], "as a matter of the sound administration of justice," the district court "is better positioned" to decide whether a case is exceptional, *id.*, at 559–560, because it lives with the case over a prolonged period of time. And as in *Pierce*, the question is "multifarious and novel," not susceptible to "useful generalization" of the sort that *de novo* review provides.

Id., slip op. at 5.

II. The ultimate determination of claim term meaning is a question of law that is reviewed *de novo*, but such a determination should only be reversed if the fact findings upon which it is based are clearly erroneous, or if the district court misapplied established Federal Circuit or Supreme Court precedent.

Patents are legal documents, and the interpretation of legal documents is a question of

law. *See Markman*, 370 at 388 ("'A patent is a legal instrument, to be construed, like other legal instruments, according to its tenor.'" (quoting 2 W. C. ROBINSON, THE LAW OF PATENTS FOR USEFUL INVENTIONS § 732 (1890))); *Levy v. Gadsby*, 7 U.S. (3 Cranch) 180, 186 (1805) (Marshall, C.J.) ("in this case the question arises upon, a written instrument, and no principle is more clearly settled, than that the construction of a written evidence is exclusively with the court"); *Eddy v. Prudence Bonds Corp.*, 165 F.2d 157, 163 (2d Cir. 1947) (Learned Hand, J.) ("[A]ppellate courts have untrammelled power to interpret written documents.").

On appeal, questions of law are reviewed *de novo*. *Pierce*, 487 U.S. at 558. Thus, while fact findings underlying claim construction should be reviewed for clear error, the final conclusion as to the proper meaning of a claim term is a question of law that should be reviewed *de novo*—claim terms are part of a legal document, a patent.

By analogy, this Court mandates a hybrid approach when reviewing a district court's obviousness determination. *See Dennison*, 475 U.S. at 810–11; *KSR Int'l*, 550 U.S. at 427; *Graham*, 383 U.S. at 17. A district court's fact findings during an obviousness analysis includes its review of the scope and content of the prior art, the differences between the prior art and the asserted claims, and the level of ordinary skill in the pertinent art. *KSR*

Int'l, 550 U.S. at 427; *Graham*, 383 U.S. at 17. Upon appellate review, this Court requires that the district court's fact findings be reviewed under Rule 52(a) for clear error. *Dennison*, 475 U.S. at 810–11. But the ultimate question of obviousness—whether a claim would have been obvious to one of ordinary skill in the art at the time of invention—is a question of law that is reviewed *de novo*. *KSR Int'l*, 550 U.S. at 427; *Graham*, 383 U.S. at 17.

The ultimate question in claim construction is the meaning that is attributed to a claim term by a person of ordinary skill in the relevant art at the time of the invention. And that meaning may be informed by subsidiary fact findings. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1332 (Fed. Cir. 2005) (Mayer, J., dissenting) ("While this court may persist in the delusion that claim construction is a purely legal determination, unaffected by underlying facts a claim should be interpreted from the perspective of one of ordinary skill in the art and in view of the state of the art at the time of invention. These questions, which are critical to the correct interpretation of a claim, are inherently factual.")

Thus, like obviousness determinations, this Court should require the Federal Circuit to apply a similar hybrid fact/law standard of review when reviewing claim construction rulings. Under this standard, the Federal Circuit could not reverse a district court's claim construction unless the court's

factual basis is clearly erroneous, or the district court misapplied established appellate claim construction precedent under a *de novo* review.

III. The meaning that a person of ordinary skill in the art would have given a claim term at the time of invention is not a historical fact.

The Federal Circuit in *Lighting Ballast* aptly noted that Rule 52(a) prescribes the standard of review for questions of fact. *Lighting Ballast*, 744 F.3d at 1290. The Federal Circuit further stated that courts must look outside the Rule to decide if a question is properly characterized as one of fact. *Id.* As this Court has recognized, drawing lines between questions of law and fact can be difficult: "Rule 52(a) does not furnish particular guidance with respect to distinguishing law from fact. Nor do we yet know of any other rule or principle that will unerringly distinguish a factual finding from a legal conclusion." *Pullman–Standard*, 456 U.S. at 288; *Cooter & Gell v. Hartmarx Corp.*, 496 U.S. 384, 401 (1990) ("The Court has long noted the difficulty of distinguishing between legal and factual issues."); *Miller*, 474 U.S. at 113–14 ("Perhaps much of the difficulty in this area stems from the practical truth that the decision to label an issue a 'question of law,' a 'question of fact,' or a 'mixed question of law and fact' is sometimes as much a matter of allocation as it is of analysis."). This

Court has also made clear that the "vexing nature" of distinguishing law from fact "does not, however, diminish its importance, or the importance of the principles that require the distinction to be drawn in certain cases." *Bose*, 466 U.S. at 501.

Various fact issues may be resolved during the process of interpreting the meaning of claim terms. These fact issues may include the pertinent field of invention and the level of ordinary skill in the art for that field. In the present case, the different ways that skilled artisans could have characterized the average molecular weight of polypeptide mixtures (e.g., peak average, number average, or weight average) in the patent claims is an example of a fact issue that the district court would have resolved. How skilled artisans could have measured the different average molecular weights, and the relative ease or difficulty with which these different averages could be obtained are also fact issues for the district court's resolution. And the district court's findings for such fact issues should only be reversed if clearly erroneous under Rule 52(a).

Some, including the petitioners in this case, have suggested that the meaning that would have been given to a claim term by a person of ordinary skill in the art at the time of invention is a "historical fact." Pet. for Writ of Cert. at 23. And that a district court's ultimate conclusion as to this meaning should also be treated as a fact finding subject to clear error review under Rule 52(a). *Id.*

The Federal Circuit in *Lighting Ballast* vigorously rejected this suggestion:

> This is not a question of fact; it is the very inquiry which determines the claim construction in nearly all cases. Claim terms are given their ordinary meaning to one of skill in the art, unless the patent documents show that the patentee departed from that meaning. Treating the ordinary meaning to a skilled artisan as requiring deference would mean deference on the controlling question of claim construction in nearly every case.

Lighting Ballast, 744 F.3d at 1289 (internal citations omitted).

One could argue that determining the meaning of a claim term from the perspective of a "person of ordinary skill in the art at the time of invention" requires forming a baseline understanding of the technology in dispute. *See* Pet. for Writ of Cert. at 18–19. One could also argue that viewing claim meaning through the lens of a person of ordinary skill in the art justifies clear error review.

But viewing a claim term's meaning through the lens of a person of ordinary skill in the art should not characterize that inquiry as a pure question of fact; it should lead to a hybrid fact/law review of a district court's claim construction.

IV. Policy considerations further support a hybrid approach to appellate review of claim construction rulings.

The private and public costs of the Federal Circuit's current *de novo* review of final claim construction definitions are high. Professor Peter Menell summarizes these costs as including:

- lower quality decision-making at both the district and appellate levels;
- higher costs of litigation resulting from too many appeals and retrials following reversals;
- greater litigation uncertainty;
- fewer and delayed settlements resulting from longer case pendency and litigation;
- the distraction and disruption of [extended] litigation on the technology marketplace; and
- unnecessarily added burdens on judges and the judicial system.

Brief of Professor Peter S. Menell as *Amicus Curiae*, *Lighting Ballast Control, LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272 (Fed. Cir. 2014) (en banc), at 16–17, available at:

http://www.grayonclaims.com/storage/Menell%20Amicus%20Brief%20Dkt.%20No.%20278.pdf.

In contrast, advantages of a "balanced, structurally sound, legally appropriate, hybrid standard of appellate review" (i.e., a standard toward which this Court's *Markman* decision points) would promote "more accurate, efficient patent dispute resolution." *Id.* at 3. Specific advantages include:

- fewer reversals and remands;
- less fear of reversal due to factual disagreements at the Federal Circuit;
- more complete and thorough claim construction orders detailing fact findings for the parties and for Federal Circuit's review;
- improved utilization of district court resources; and
- increased settlements.

Id.

This Court has long-recognized the importance of uniformity in the treatment of patents as an additional reason for allocating claim construction issues to the district judge, and for reviewing final claim term definitions *de novo*, but with deference

to the district court's fact findings. Professor Menell's assessments provide this Court additional, prudential reasons for requiring a hybrid fact/law approach when reviewing claim construction rulings.

CONCLUSION

HIPLA respectfully asks this Court to rule that: (1) a district court's fact findings during claim construction is entitled to deferential review under the clearly erroneous standard of Rule 52(a); (2) a district court's final claim term definition is subject to *de novo* review; (3) a claim term definition should not be overturned unless the fact findings upon which the definition is based are clearly erroneous, or unless the district court misapplied settled claim construction precedent; and (4) the meaning attributable to a claim term by one of ordinary skill in the art at the time of invention is not a historical fact entitled to deferential review.

Respectfully submitted,

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JUNE 20, 2014

AMICUS CURIAE BRIEF

No. 13-854

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,
Petitioners,

v.

SANDOZ, INC., ET AL.,
Respondents.

On Writ Of Certiorari
To The United States Court Of Appeals
For The Federal Circuit

BRIEF FOR INTEL CORPORATION, EMC CORPORATION, FACEBOOK, INC., RED HAT, INC., AND VERIZON COMMUNICATIONS INC. AS *AMICI CURIAE* IN SUPPORT OF AFFIRMANCE

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QUESTION PRESENTED

Whether Federal Rule of Civil Procedure 52(a) requires an appellate court to defer to district court determinations on the "purely legal" issue of claim construction. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996).

RULE 29.6 STATEMENT

Intel Corporation has no parent, and no publicly held company owns 10% or more of its stock.

EMC Corporation has no parent, and no publicly held company owns 10% or more of its stock.

Facebook, Inc. has no parent, and no publicly held company owns 10% or more of its stock.

Red Hat, Inc., has no parent. T. Rowe Price Associates Inc. and Jennison Associates LLC each own over 10% of Red Hat, Inc.'s outstanding shares. Prudential Financial, Inc., a public company, is the parent of Jennison Associates LLC.

Verizon Communications Inc. has no parent, and no publicly held company owns 10% or more of its stock.

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INTEREST OF THE *AMICI CURIAE*[1]

Amici are a diverse group of technology companies. Together, they own thousands of patents worldwide and provide many of the most innovative products and services on the market today. As the manufacturers, sellers, or providers of products and services that incorporate hundreds or even thousands of technologies, *amici* are potential defendants in infringement suits, many involving patent claims of highly questionable validity. On the other hand, as owners of significant patent portfolios, *amici* are acutely aware of the importance of a strong and consistent system for protecting intellectual property. *Amici* thus understand better than most the importance of a balanced patent system to furthering innovation.

Clear notice of what is claimed in a patent is essential to that balance. Well-defined claims reward patentees for the inventions they contribute, while incentivizing competitors to innovate around the readily discernible boundaries of the claim. Vague claims create legal uncertainty that discourages design-around efforts and thus both dampen innovation and unjustly enrich the patentee with a zone of exclusivity that exceeds its inventive contribution. *Nautilus, Inc.* v. *Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). Predictable and uniform construction of claims—achieved through a single appellate court's *de novo* review of district court claim constructions—operates as a significant check on the le-

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[1] All parties have consented to the filing of this brief. No counsel for any party authored this brief in whole or in part, and no person or entity, other than *amici* or their counsel, made a monetary contribution intended to fund the preparation or submission of this brief.

gal uncertainty generated by vague claims, and an important protection against the ability of patent holders to select forums perceived as particularly favorable to broad construction of patent claims.

Amici have a strong interest in ensuring that vague claims are not further exploited through a regime of appellate deference to inconsistent claim constructions. The uncertainty inherent in a patent system that permits inconsistent claim constructions makes it more difficult for *amici* and other innovative companies to develop and deploy new technologies. Moreover, as those companies' increasingly common experience shows, uncertainty wastes resources in litigation that becomes more expensive and more difficult to resolve.

SUMMARY OF THE ARGUMENT

This Court has held that claim construction presents a "purely legal" issue to be resolved by the courts. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996). The interpretation of unambiguous written instruments has long been viewed as a legal issue to be reviewed *de novo* on appeal. Hence, the Federal Circuit repeatedly has reaffirmed that claim construction should receive independent appellate review. *See Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448, 1454–55 (Fed. Cir. 1998) (en banc); *Lighting Ballast Control LLC* v. *Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1276–95 (Fed. Cir. 2014) (en banc), *petition for cert. filed*, No. 13-1536 (June 20, 2014). Any departure from that standard would be inconsistent with this Court's clear and controlling precedent. It also would undermine Congress's overriding goal in creating a single court of appeals with jurisdiction over all cases arising under

the patent laws—to bring greater uniformity to patent decisions. Deferential review risks application of inconsistent claim constructions in district courts around the country, and encourages unscrupulous patentees to shop for a favorable forum. And treating claim-construction issues as questions of fact, even in part, would swamp the district courts and the Federal Circuit with more intensive subsidiary litigation over the factual or legal nature of particular determinations. Vagueness in claims might improperly be treated as raising questions of fact to be addressed through inventor or expert testimony. But if a claim cannot be construed based on the patent, its file history, and objective contemporaneous evidence of meaning (such as dictionaries and treatises), it should be held indefinite, not used to engender a trial within a trial that generates purported findings of "fact" to which an appellate court must defer.

As the appellate court for all patent issues—arising from 94 district courts, the Patent and Trademark Office, and the International Trade Commission—the Federal Circuit is uniquely suited to provide uniform interpretation of technical patents. It should review district court claim-construction decisions without deference.

ARGUMENT

I. *Markman's* Treatment Of Claim Construction As A Legal Issue Dictates *De Novo* Review

A. This Court Has Held That Claim Construction Is A Legal Issue, For The Court Alone

In *Markman*, this Court addressed whether to view claim construction, in its entirety, as an issue of law or fact. Precedent long had held that "[q]uestions of construction are *questions of law* for the judge, not questions of fact for the jury." *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 387 (1996) (quoting Albert H. Walker, *Patent Laws* § 189, at 173 (3d ed. 1895)) (emphasis added). But even though the Court's earliest decisions had held that "construing the letters-patent" is "a question of law, to be determined by the court" (*Winans* v. *Denmead*, 56 U.S. (15 How.) 330, 338 (1854)), the patentee in *Markman* argued that this principle did not apply when expert testimony was at issue (517 U.S. at 385–86). Hence, this Court faced a dichotomous question: whether claim construction "is a *matter of law* reserved entirely for the court, or subject to a Seventh Amendment guarantee that a jury will determine the meaning of any disputed term of art about which expert testimony is offered." *Id.* at 372 (emphasis added). The Court unanimously held that the former view was correct. Adhering to past precedent, including the conclusion of Justice Curtis, a former patent practitioner, who declared for this Court more than a century ago that claim construction "'is a question of law, to be determined by the court'" (*id.* at 384, 388 (citation omitted)), the *Mark-*

man Court unanimously reaffirmed that long-established principle, and accordingly concluded that "the construction of a patent, including terms of art within its claim, is exclusively within the province of the court." *Id.*

The Court reasoned that the particular nature of claim construction makes it better suited for resolution by judge than by jury. Because the "construction of written instruments is one of those things that judges often do and are likely to do better than jurors unburdened by training in exegesis," it is "judges, not juries," that "are the better suited to find the acquired meaning of patent terms." *Markman*, 517 U.S. at 388. The Court observed that "[p]atent construction in particular is a special occupation" that merits "special training and practice," and concluded that a judge "is more likely to give a proper interpretation to such instruments than a jury; and he is, therefore, more likely to be right, in performing such a duty, than a jury can be expected to be." *Id.* at 388–89 (quotation marks omitted).

The Court also emphasized "the importance of uniformity in the treatment of a given patent as an independent reason to allocate all issues of construction to the court." *Markman*, 517 U.S. at 390. "It was just for the sake of such desirable uniformity that Congress created the Court of Appeals for the Federal Circuit as an exclusive appellate court for patent cases." *Id.* Review by a single court of appeals, and in particular the Federal Circuit's ability to "subject" claim construction "questions" to the rule of prior precedent, is critical "to interjurisdictional uniformity." *Id.* at 391.

Hence, this Court held, "in the actual interpretation of the patent *the court proceeds upon its own re-*

sponsibility, as an *arbiter of the law*, giving to the patent its true and final character and force." *Markman*, 517 U.S. at 388 (citation omitted; emphasis altered). The court's independent responsibility to resolve legal issues takes on added force in the claim-construction context because a patent is a legal instrument, binding on the public like a statute or regulation. *Id.* Thus "the instrument as a whole" must be the focus of claim construction, and other sources are of "doubtful" weight. *Id.* at 389. Were construction to turn on other factors, a "zone of uncertainty" would result, thus hampering innovation. *Id.* at 390 (citation omitted).

Therefore, "treating interpretive issues as *purely legal*"—and thus *not* as a mixed question of law and fact—is the proper approach. *Markman*, 517 U.S. at 391 (emphasis added). What petitioners call the Federal Circuit's "notion"—"that patents are written instruments and must be construed purely as a matter of law" (Pet. Br. 41)—is in reality *Markman*'s resolution of the question it faced. *Markman* explicated this Court's methodology "to classify a mongrel practice" as an issue of either "fact" or "law" (517 U.S. at 378): When an issue "falls somewhere between a pristine legal standard and a simple historical fact," this Court will investigate whether "one judicial actor is better positioned than another to decide the issue in question." *Id.* at 388 (quoting *Miller* v. *Fenton*, 474 U.S. 104, 114 (1985)). The best "allocation" of decision-making then determines whether the decision is made by the court or by the finder of fact. *Miller*, 474 U.S. at 113. In *Markman*, this Court undertook that investigation, and concluded that viewing claim construction as an issue of law would bring consistency and ensure the "sound administration of justice." *Markman*, 517 U.S. at 388–39 (citation

omitted). *Markman*'s prefatory "mongrel practice" remark thus merely posed the question that its holding answered: Claim construction "is a question of law, to be determined by the court." *Id.* at 378, 384 (citation omitted).

Given this Court's holding that claim construction must be considered a "purely legal" issue, the Federal Rules of Civil Procedure do not permit it to be treated as an issue of fact. Rule 52 provides that "[f]indings of fact" can only "be set aside" if "clearly erroneous," but merely because a district court *labels* its conclusion a "finding" does not make it so for purposes of Rule 52. *See Lockhart* v. *McCree*, 476 U.S. 162, 168 n.3 (1986) (this Court was "far from persuaded" that the district court's supposed "'factual' findings" warranted deference under Rule 52(a)(6)). This Court instead must decide whether the issue the district court decided was truly a "question[ ] of law" or a "question[ ] of fact." *Pullman-Standard* v. *Swint*, 456 U.S. 273, 288 (1982). *Markman* conclusively resolved that inquiry for claim construction. Where the determination really is a "conclusion[ ] of law" (*id.* at 287)—as this Court has declared claim construction to be (*Markman*, 517 U.S. at 391)—then "[t]he Rule does not apply" (*Swint*, 456 U.S. at 287).

B. Questions Of Law, Reserved For The Court Alone, Receive *De Novo* Review On Appeal

Questions of law receive *de novo* review. "Traditionally, decisions on questions of law are reviewable *de novo*, decisions on questions of fact are reviewable for clear error, and decisions on matters of discretion are reviewable for abuse of discretion." *Highmark Inc.* v. *Allcare Health Mgmt. Sys., Inc.*, 134 S. Ct.

1744, 1748 (2014) (quotation marks omitted). This Court thus explained in *Salve Regina College* v. *Russell*, 499 U.S. 225 (1991), that "[i]ndependent appellate review of legal issues best serves the dual goals of doctrinal coherence and economy of judicial administration." *Id.* at 231. These two objectives are intertwined: The speed with which district courts must decide legal issues limits "the extent to which trial counsel is able to supplement the district judge's legal research." *Id.* By contrast, "appellate judges are able to devote their primary attention to legal issues" and benefit from the "reflective dialogue and collective judgment" that come with appellate "multijudge panels." *Id.* at 232. This leads to improved accuracy in decision-making. *Id.* And, when coupled with the controlling effect *stare decisis* accords to their decisions, plenary review by multijudge panels ensures consistent application of those legal determinations. These rationales for *de novo* review of questions of law apply with full force to claim construction, and compel the conclusion that *de novo* review is appropriate in light of this Court's unchallenged holding in *Markman* that questions of claim construction are "purely legal" in nature. 517 U.S. at 391.

Even if claim construction could (despite *Markman*) be regarded as a mixed question of law and fact, moreover, much the same reasoning would dictate plenary appellate review. As this Court has explained, even where the issue "is a mixed question of law and fact," the need for "appellate courts" to "maintain control of, and to clarify, the legal principles" often requires "independent appellate review." *Ornelas* v. *United States*, 517 U.S. 690, 696–97 (1996). Indeed, an issue may require "plenary feder-

al review," in spite of its "hybrid quality." *Miller*, 474 U.S. at 112, 116.

Deferential review is particularly inappropriate in the context of claim construction because patents are effectively a government grant of a right to exclude. This Court has recognized that land patents, which are also federal property grants, provide a good analogy to utility patents. *See Markman*, 517 U.S. at 382–83 (the "practice of interpreting terms within a land patent" too "fell to the judge, not the jury"). And *Markman* cited with approval a nineteenth-century case holding that the "construction" of a land patent, like that of a utility patent, is "within the exclusive province of the court." *Brown* v. *Huger*, 62 U.S. (21 How.) 305, 318 (1859); *see also id.* at 318–22 (applying plenary review to land patent). Indeed, this Court later analogized utility patent claims to deeds for real property, observing that a patent claim, because it "mark[s] where the progress claimed by the patent begins and where it ends," sets the bounds to the grant which it contains. *Motion Picture Patents Co.* v. *Universal Film Mfg. Co.*, 243 U.S. 502, 510 (1917). And appellate courts universally "review the District Court's interpretation of the deed *de novo*." *Wash. Metro. Area Transit Auth.* v. *Georgetown Univ.*, 347 F.3d 941, 945 (D.C. Cir. 2003); *accord, e.g.*, *EnerVest Operating, LLC* v. *Sebastian Mining, LLC*, 676 F.3d 1144, 1146 (8th Cir. 2012).[2]

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[2] Moreover, the construction of other analogous legal instruments, like regulations and statutes, is likewise reviewed without deference. Indeed, appellate courts routinely examine and decide underlying questions that can be described as "factual" on their own and without deference to district courts. *See, e.g.*, *Markman*, 517 U.S. at 378–84 (analyzing the historical record

Claim construction is of a piece with the interpretation of other unambiguous written instruments, which invariably is regarded as a pure issue of law. Against this background, there is no justification for departing from the independent appellate review prescribed for legal issues in *Salve Regina*.

II. Independent Appellate Review Furthers The Interrelated Goals Of Uniform Decisionmaking, Clear Notice, And Accurate Interpretations

Plenary review of claim construction also serves worthy policy goals. Most importantly, *de novo* review ensures consistent, accurate constructions of claim language—whereas deferential review could mandate affirmance of contradictory interpretations of the same patent claim in different cases. *Lighting Ballast Control LLC* v. *Philips Elecs. N. Am. Corp.*, 744 F.3d 1272, 1287–88 (Fed. Cir. 2014) (en banc). The resulting uncertainty and possible legal contradiction across multiple cases and extending over the entire life of each patent would be far worse than any temporary delay in certainty attributable to the availability of *de novo* appellate review the first time an issue of claim construction arises. Deference also would increase the claim-construction stakes in the district court, incentivizing litigants to create detailed "factual" records to support their preferred claim constructions, driving up litigation costs and increasing consumption of scarce judicial resources. The proper means of ensuring accuracy in the district court and reducing claim-construction reversals is not to expand the scope of construction disputes,

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to determine whether, in the 18th and 19th centuries, juries or judges decided the meaning of claim terms).

but to reduce them. More vigorous enforcement of the requirement of claim definiteness can achieve this policy goal. *See Nautilus, Inc.* v. *Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). Deference to district court claim constructions, on the other hand, will serve only to regularize inconsistent and erroneous claim-construction decisions, undermining the very rationale for creation of the Federal Circuit and further eroding confidence that the patent system is producing accurate results.

A. Congress Created The Federal Circuit To Ensure Clear, Uniform, And Accurate Resolution Of Legal Issues

Congress's key reason for creating a single intermediate appellate court to review all cases arising under the patent laws (28 U.S.C. § 1295(a)) was that "patent cases are inconsistently adjudicated," producing "inconsistent" outcomes. S. Rep. No. 97-275, at 3, 5 (1981), *reprinted in* 1982 U.S.C.C.A.N. 11. Congress established the Federal Circuit to craft a "more stable and predictable" patent law, an area with a "special need for national uniformity." *Id.* at 4, 6. That court would operate as a "forum for the definitive adjudication" of legal issues governing patents. *Id.* at 3.

This Court has recognized the "importance" and applicability of consistency in the claim-construction context: "It was just for the sake of such desirable uniformity that Congress created the Court of Appeals for the Federal Circuit as an exclusive appellate court for patent cases." *Markman*, 517 U.S. at 390. Practitioners and patentees rely on the single court of appeals' consistent application of the law across all federal district courts, the Patent Trial and

Appeal Board, and the International Trade Commission. *See Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 162 (1989) ("Congress conferred exclusive jurisdiction of all patent appeals on the Court of Appeals for the Federal Circuit in order to provide nationwide uniformity in patent law.") (punctuation omitted). This Court explained that Federal Circuit review reduces the "zone of uncertainty" surrounding a patent claim's application to technology. *Markman*, 517 U.S. at 390. Such uncertainty chills competitors—even those who do not actually practice the claimed invention, properly construed—due to the threat of vague "infringement claims." *Id.* (quotation marks omitted). Indeed, this Court observed, these lawsuits "discourage invention only a little less than unequivocal foreclosure of the field." *Id.* (quotation marks omitted). A clear, uniform, and binding claim construction that definitively construes the disputed claim terms for the entire life of the patent is crucial to ensure that the public is not "deprived of rights supposed to belong to it, without being clearly told what it is that limits these rights." *Id.* (quotation marks omitted).

B. *De Novo* Review Is Essential For Consistent Constructions That Clearly Delineate The Patent's Scope

De novo review is essential to clear, uniform, and definitive claim constructions. Only plenary review can ensure that a claim is construed consistently; application of a clear-error standard of review would inevitably generate disparate interpretations of the same patent claims in different cases.

1. Independent Appellate Review Is Needed For Uniformity

This Court has explained that the compelling need for uniformity in the administration of patents was a principal reason for treating claim construction in its entirety as an issue of law: "treating interpretive issues as *purely legal* will promote (though it will not guarantee) intrajurisdictional certainty through the application of *stare decisis*." *Markman*, 517 U.S. at 391 (emphasis added). In *Lighting Ballast*, the Federal Circuit confirmed that "the possibility of disparate district court constructions unravels the 'uniformity in the treatment of a given patent' that the Court sought to achieve in *Markman*." 744 F.3d at 1286 (quoting *Markman*, 517 U.S. at 390); *accord id.* at 1292–93 (Lourie, J., concurring).

As one commentator explains, "treating claim construction as a matter of binding legal precedent rather than a factual issue that must be reexamined anew when new parties litigate a patent for the first time" advances "uniformity in how a given patent is construed," which in turn enhances "the public interest in knowing the scope of patent claims." David Krinsky, *The Supreme Court, Stare Decisis, and the Role of Appellate Deference in Patent Claim Construction Appeals*, 66 Md. L. Rev. 194, 204 (2006). In fact, *Markman* stated its expectation that "the single appeals court" (*i.e.*, the Federal Circuit) would ensure "uniformity" and "certainty" by applying its claim-construction decisions to future cases as a matter of *stare decisis*. 517 U.S. at 391. In independently reviewing district court claim constructions, the Federal Circuit has followed this command, noting that "for us not to adopt the same claim construction in a case such as this would run counter to the

Supreme Court's guidance on stare decisis in *Markman*." *Miken Composites, LLC* v. *Wilson Sporting Goods Co.*, 515 F.3d 1331, 1338 n.* (Fed. Cir. 2008).

But "the application of *stare decisis*" to claim-construction decisions as contemplated in *Markman* (517 U.S. at 391) simply cannot occur under a regime of deferential review. As the Federal Circuit warned, "differing district court rulings on close questions of claim construction could well warrant affirmance on deferential review." *Lighting Ballast*, 744 F.3d at 1286. Indeed, a panel's holding that a district court did not *clearly* err is not even necessarily instructive—much less controlling—regarding the separate question whether a second district court's inconsistent construction was itself *clearly* erroneous. Thus, with deferential review, the Federal Circuit might adopt "conflicting claim constructions, the antithesis of uniformity." *Id.* at 1293 (Lourie, J., concurring).

This possibility is real. For example, in one recent case, *seven* district courts construed three terms from the same patent, and "no two ha[d] construed all three terms the same way." *Am. Piledriving Equip., Inc.* v. *Geoquip, Inc.*, 637 F.3d 1324, 1327 & n.1 (Fed. Cir. 2011); *see also, e.g.*, Appellant's Reply Br., *Alcatel-Lucent USA Inc.* v. *Overstock.com, Inc.*, 505 F. App'x 957 (Fed. Cir. 2013) (per curiam) (No. 2012-1629), 2013 WL 950401, at *24 (noting that "three district courts construed" a term "in *different* ways based on *different* interpretations of the prosecution history"). In *American Piledriving*, the Federal Circuit was able to consolidate the appeals, affirm the correct construction and reverse the incorrect construction (637 F.3d at 1337), which might not have been possible had the court been obliged to con-

duct deferential review. Divergent constructions are even more likely now that the America Invents Act has required plaintiffs to pursue separate lawsuits aimed at different individual defendants rather than joining multiple defendants in a single lawsuit. *Lighting Ballast*, 744 F.3d at 1293 (Lourie, J., concurring).

Such a result would be pernicious: Researchers have found that heavily litigated patents, with infringement suits spanning multiple districts, tend to be of lower quality. John R. Allison et al., *Patent Quality and Settlement Among Repeat Patent Litigants*, 99 Geo. L.J. 677, 687–88, 709 (2011). Venue transfers are no solution; district courts have denied motions to transfer litigation over related patents into a single district. *See Document Generation Corp.* v. *Allscripts, LLC*, No. 6:08-CV-479, 2009 WL 2824741, at *2 (E.D. Tex. Aug. 27, 2009).

Indeed, as this Court recognized, even principles of *res judicata* are of limited utility because "issue preclusion could not be asserted against new and independent infringement defendants." *Markman*, 517 U.S. at 391. Under a deferential regime, a new defendant in a follow-on case would not be bound by the Federal Circuit's previous construction of a particular claim, but could re-litigate the issue in the district court and on appeal simply by offering evidence supporting a different construction. This possibility of "the same patent, asserted in different district court jurisdictions" being construed in different ways strongly counsels in favor of uniform appellate review. *Biodex Corp.* v. *Loredan Biomedical, Inc.*, 946 F.2d 850, 859 (Fed. Cir. 1991).

2. Uncertain Claim Construction Raises The Costs Of Litigation And Hampers Innovation

A system that creates the possibility of inconsistent claim constructions and invites re-litigation of the same interpretive issues in case after case is not a sustainable means of adjudicating rights and obligations under government grants, effective against *everyone in the Nation*. For this reason, the Federal Circuit, as a court "of nation-wide jurisdiction, should continue to review claim construction *de novo* with national effect." *Lighting Ballast*, 744 F.3d at 1286. The patentee, its competitors, and the public all require clear and certain demarcation of the rights granted by the patent if they are to be expected to order their affairs around it. As in any property-rights regime, readily discernible and consistent boundaries are necessary for the success of the participants and ultimately the regime itself. R. H. Coase, *The Problem of Social Cost*, 3 J.L. & Econ. 1, 19 (1960) ("[A]ll that matters (questions of equity apart) is that the rights of the various parties should be well-defined and the results of legal actions easy to forecast."). When property rights are not clearly defined or are constantly subject to revision, unintentional trespasses are inevitable, public respect for property rights erodes, and the system eventually breaks down. Competing and inconsistent interpretations of patent claims obscure the boundaries of patents and deeply undermine their important notice function, inevitably resulting in more—rather than less—litigation.

Not only will litigation increase; it could also become even more difficult to resolve expeditiously in the district court. If claim construction is regarded

as involving questions of fact, then it could be harder to obtain early summary judgment, dismissal, or other resolutions before intensive discovery begins; some courts may opt to delay claim construction (and summary judgment) until near the end of the case, after extensive fact and expert discovery—forcing parties to litigate for years without a judicial determination of the meaning of the patent claims being asserted. This will increase the expense of litigation, as well as promote the abuse of discovery as a harassment tool to wield against opposing parties. The courts' experience in the qualified-immunity context is instructive: When this Court recognized that qualified immunity was an issue of law, the courts saw more "early" resolution of disputes through "summary judgment," and parties were "spar[ed]" the "expense and burden of extensive discovery." Michele L. Hammers, *Heightened Pleading Standards in Civil Rights Cases Against Municipalities*, 1 Tex. F. on C.L. & C.R. 13, 14 (1993). Thus, treating claim-construction issues as fact questions would have the opposite effect, pushing patent litigation further down the path towards ever more lengthy, costly, and abusive litigation. Treating claim construction as a question of law is essential to fostering a less burdensome and more efficient system of patent litigation in the United States.

Deferential review, by contrast, "would restore the forum shopping that the Federal Circuit was created to avoid." *Lighting Ballast*, 744 F.3d at 1286. Plaintiffs select their forum in part on the basis of the district court's claim-construction practices, including whether (and at what point in the case) the court typically holds *Markman* hearings and "the type of evidence the judges will consider in construing the claims." Kimberly A. Moore, *Forum Shop-*

ping in Patent Cases: Does Geographic Choice Affect Innovation?, 79 N.C. L. Rev. 889, 900 (2001). In a deferential regime, these sorts of differences would take on much greater import. If a district court's claim construction were insulated from plenary review, plaintiffs could select a forum based on the court's perceived tendency to approach claim construction in a manner favorable to them, secure in the knowledge that any beneficial claim construction would likely be upheld on appeal. *See* Yan Leychkis, *Of Fire Ants and Claim Construction: An Empirical Study of the Meteoric Rise of the Eastern District of Texas as a Preeminent Forum for Patent Litigation*, 9 Yale J.L. & Tech. 193, 216 (2007) (providing data that judges in some districts are more pro-patentee than others).

Although the Federal Circuit has enhanced substantive uniformity in patent law to some extent, "[f]orum shopping remains rampant in patent litigation." Tesera Lii, *Shopping for Reversals: How Accuracy Differs Across Patent Litigation Forums*, 12 Chi.-Kent J. Intell. Prop. 31, 34 (2013). Patentees have flocked to districts that studies have shown are "overwhelmingly plaintiff-friendly, in both the likelihood of a verdict favoring the plaintiff, as well as the size of the damages awarded to that plaintiff." *Id.* at 37; *accord* Chester S. Chuang, *Offensive Venue: The Curious Use of Declaratory Judgment to Forum Shop in Patent Litigation*, 80 Geo. Wash. L. Rev. 1065, 1073 & n.46 (2012) (collecting studies showing that this "rampant forum shopping" arises because "the outcome of the case often turns on the choice of forum," an effect that Federal Circuit review has mitigated).

The "explosion of forum shopping in present-day patent litigation" is thus the result of the fact that "jurisdictional equality in patent litigation" is simply "not to be had" in the federal district courts. Lii, *supra*, at 34–35. That problem would be greatly exacerbated, however, if claim construction rulings were subjected to deferential review. Even under the present regime of *de novo* appellate review, which offers litigants a reasonable opportunity to overturn faulty claim constructions, a district court's claim construction ruling "is so important to patent litigation that once the court construes the claims, most patent cases settle." Mark A. Lemley, *The Changing Meaning*, 104 Mich. L. Rev. 101, 102 (2005); *see also id.* at 102 n.4.

The "industry" of entities who "use patents not as a basis for producing and selling goods but, instead, primarily for obtaining licensing fees" (*eBay Inc.* v. *MercExchange, L.L.C.*, 547 U.S. 388, 396 (2006) (Kennedy, J., concurring)) is especially likely to exploit forum-shopping opportunities in this manner. Non-practicing entities easily can and do establish their place of incorporation and putative headquarters in a forum perceived as favorable, in order to manufacture venue. *See, e.g.*, *In re Zimmer Holdings, Inc.*, 609 F.3d 1378, 1381 (Fed. Cir. 2010). *Amici* have seen the significant costs of such litigation tactics firsthand. Moreover, even in the rare instances where an accused infringer can overcome justiciability hurdles and initiate a declaratory judgment action seeking a determination of non-infringement and/or invalidity, accused infringers are more likely to lose venue contests with patent holders. Chuang, *supra*, at 1069, 1083-87.

As Kimberly Moore, now a Federal Circuit judge, has rightly explained, forum shopping imposes numerous costs: it "erodes public confidence in the law"; "wastes resources by increasing litigation costs"; and "decrease[s] innovation" by chilling competitors, who will "systematically over-comply with the scope of the patent holder's exclusive right, consistently expanding the property right beyond what was intended when the patent was granted." Moore, *supra*, at 924–30. Other commentators note additional ill effects of forum shopping, including that it "confounds and complicates litigation by selectively creating pockets of district courts that apply the law in a nonuniform manner." Lii, *supra*, at 39. Mandating deference to patentee-friendly district courts is especially problematic because such districts have "a greater likelihood of adjudicating cases inaccurately." *Id.* at 48.

Congress created the Federal Circuit in part to remedy the problems that forum shopping among the regional circuits had caused. *See* Larry D. Thompson, Jr., *Adrift on a Sea of Uncertainty: Preserving Uniformity in Patent Law Post-*Vornado *Through Deference to the Federal Circuit*, 92 Geo. L.J. 523, 529–33 (2004). Weakening the single appellate court's "control of" the "legal principles" (*Ornelas*, 517 U.S. at 697) behind claim construction would undermine this goal and multiply the problems caused by forum shopping, diminishing public confidence in the patent system. Notably, petitioners do not address the forum-shopping problems that deferential review would exacerbate.

C. Trial Judges' Access To In-Person Evidence Is Of Little Relevance To Claim Construction, Particularly In Comparison To The Importance Of Clearly Defining The Scope Of The Patent Grant

Petitioners argue that district courts have better access to "evidence" in "the record" and that this counsels in favor of deference. Pet. Br. 20–25. But patents and their prosecution histories are written documents that are just as accessible to an appeals court (which may have more time to consider them) as to a district court. The only evidence in a typical patent case that a district court alone can observe is a live witness's demeanor—and, as this Court has explained, the importance of witness credibility to claim construction is "doubtful" at best. *Markman*, 517 U.S. at 389. Claim construction, like the construction of other written instruments, rarely turns on "a simple credibility judgment" used "to choose between experts whose testimony was equally consistent with a patent's internal logic." *Id.* Moreover, three heads are better than one when it comes to evaluating expert opinion on a definition of the bounds of a government property grant that affects competition and innovation. The use of "multijudge panels" has the salutary effect of "permit[ting] reflective dialogue and collective judgment" and thereby "promotes decisional accuracy." *Salve Regina*, 499 U.S. at 232. It is for these reasons that this Court required all subsidiary claim-construction issues, including disputes involving "expert testimony," to be resolved as "a matter of law." *Markman*, 517 U.S. at 372.

Significantly, moreover, the need for accuracy and uniformity is especially great in this context.

"The claim defines the scope of a patent grant." *Markman*, 517 U.S. at 373 (punctuation omitted). Clear scope is important to *all* potential market entrants. This kind of horizontal certainty is essential to the entire affected industry. By contrast, the concern that *de novo* review increases the duration of a single patent litigation until a final decision is reached in that particular case—what might be called vertical uncertainty—matters only in the small fraction of cases that reach an appeal. Vertical uncertainty is more visible than horizontal uncertainty, but, as often is the case, here it is the unseen effects that are greater. *Cf.* Frédéric Bastiat, *What Is Seen and What Is Not Seen* (1848), *available at* http://www.econlib.org/library/Bastiat/basEss1.html.

For this reason, it is not merely the overarching principles of claim construction, but their application, that must be consistent. *Contra* Pet. Br. 47. In claim construction as elsewhere, "the relevant legal principle can be given meaning only through its application to the particular circumstances of a case." *Miller*, 474 U.S. at 114. A uniform rule does little good if district judges can construe the same term in divergent ways. A regime of *de novo* review, by contrast, ensures that important issues of claim construction are ultimately resolved in a definitive manner by multi-judge panels of the Federal Circuit, whose patent expertise particularly suits them to construe claim terms, and whose plenary review is critical to uniformity. *See* Moore, *supra*, at 927 (noting that "[u]npredictable and inconsistent application of laws traditionally has been a major concern in patent cases and was the impetus for the creation of the Federal Circuit"); Gwendolyn Dawson, *Note: Matchmaking in the Realm of Patents: A Call for the Marriage of Patent Theory and Claim Construction*

Procedure, 79 Tex. L. Rev. 1257, 1282 (2001) (arguing that the Federal Circuit's "great expertise in handling patent cases" counsels in favor of "a strict de novo standard of review" in order to "fairly decide cases").

D. Section 112 Reinforces The Importance Of Clear, Uniform Interpretation Of Patent Claims

This Court recently overturned the Federal Circuit's standard for definiteness, which had allowed claims that "lack the precision § 112, ¶ 2 demands." *Nautilus*, 134 S. Ct. at 2130. Under Section 112, "a patent must be precise enough to afford clear notice of what is claimed, thereby apprising the public of what is still open to them." *Id.* at 2129 (punctuation omitted). Definiteness "[e]liminat[es]" the "temptation" of patentees—backed by "powerful incentives"—"to inject ambiguity into their claims" and thereby assert them against technologies never contemplated when they filed their applications. *Id.*

After *Nautilus*, the Federal Circuit may reject as indefinite many claims that can be construed only by resort to extrinsic evidence, further minimizing any need for the sorts of alleged "factfinding" to which petitioners would apply deferential review. *Enzo Biochem, Inc.* v. *Applera Corp.*, 605 F.3d 1347, 1348 & n.2 (2010) (Plager, J., dissenting from denial of reh'g); *see also Markman* v. *Westview Instruments, Inc.*, 52 F.3d 967, 986 (Fed. Cir. 1995) (en banc) (section 112 "has as its purpose the avoidance of the kind of ambiguity that allows introduction of extrinsic evidence"), *aff'd*, 517 U.S. 530.

De novo appellate review can help ensure the clarity demanded by Section 112: "if the de novo re-

view process allows the Federal Circuit to establish clear guidelines for the interpretation of patent claims, certainty and efficiency would be enhanced." R. Polk Wagner & Lee Petherbridge, *Is the Federal Circuit Succeeding? An Empirical Assessment of Judicial Performance*, 152 U. Pa. L. Rev. 1105, 1124 & n.80 (2004).

This case illustrates the point. The Federal Circuit held petitioners' asserted claim invalid as lacking sufficient clarity to inform the public of what it covers. Pet. App. 8a–10a. It did so by examining the publicly available written record—the patent and its prosecution history—instead of crediting the say-so of either side's competing expert. *Id.* at 9a–10a. That was entirely proper: "the patent's specification and prosecution history" are exactly the sources that courts should examine "in assessing definiteness." *Nautilus*, 134 S. Ct. at 2128. Petitioners now complain that the Federal Circuit did not defer to the district court's conclusion that their "expert [was] more persuasive." Pet. Br. 55. But Section 112 requires claims to be clear "at the time the patent was filed," not ambiguous until clarified by an expert during litigation. *Nautilus*, 134 S. Ct. at 2128 (citation and emphasis omitted). A claim whose interpretation varies depending on the relative credibility of the paid experts proffered by opposing litigants is not a claim that provides the "reasonable certainty" required by Section 112. *Id.* at 2129.

The more rigorous definiteness requirement dictated by *Nautilus* will (if properly implemented by the Patent and Trademark Office and the Federal Circuit) ensure that claims are clear when they issue—and thereby reduce the number of disputed claim terms and make construing them less difficult.

Commentators have lamented that "[u]nclear boundaries create many of the problems of the patent system," including requiring courts to "expend more judicial resources resolving the ambiguities created by unclear boundaries," and drive up the number of appeals and reversals. Christopher A. Cotropia, *The Folly of Early Filing in Patent Law*, 61 Hastings L.J. 65, 118 (2009); *see also* Joseph A. Biela, *Claim Interpretation: A Claim Indefiniteness Analysis Proposal*, 47 IDEA 561, 573 (2007) (proposing a rigorous indefiniteness standard to "reduce the uncertainty" in claim construction); Christa J. Laser, *A Definite Claim on Claim Indefiniteness: An Empirical Study of Definiteness Cases of the Past Decade with a Focus on the Federal Circuit and the Insolubly Ambiguous Standard*, 10 Chi.-Kent J. Intell. Prop. 25, 28 (2010) (collecting empirical evidence that, before *Nautilus*, "courts ha[d] not extensively incorporated the public policy demand for the clearest possible patents into the requirement of claim indefiniteness").

According deference to district courts' claim constructions, on the other hand, would increase the frequency and intensity of claim-construction disputes, hampering the early resolution of lawsuits, without any concomitant substantial reduction in the number of claim-construction appeals. The more effective means of combating over-litigation of claim construction is not shifting the burden onto the district courts, but "shifting the focus from litigation over claim construction to clarity in claim drafting." *Enzo*, 605 F.3d at 1349 (Plager, J., dissenting from denial of reh'g).

III. Requiring A Court To Dissect Law And Fact Would Generate Further Uncertainty And Wasteful Peripheral Litigation

The correctness of this Court's determination that claim construction is "purely legal" in nature, *Markman*, 517 U.S. at 391, is confirmed by an examination of the problematic consequences that would flow from adoption of the shifting-standards approach urged by petitioners and the Solicitor General. The latter approach would require both district courts and the Federal Circuit to engage in the wasteful and ultimately fruitless task of attempting to dissect "legal" and "factual" components in some consistent and principled manner, an effort that would simply invite confusion and ancillary litigation about which sources of evidence generate "findings" and which "holdings."

For example, petitioners admit that claim construction involves some "[t]rue legal holdings," but contend that "[w]hile the ultimate interpretation of a legal document is indeed a legal question, interpretation has various ingredients, and some of those ingredients . . . are factual." Pet. Br. 32, 47. Petitioners thus would require district courts to separate the factual and legal "ingredients" in the completed claim-construction dish. *Id.* at 32.

But petitioners, like the deference advocates in *Lighting Ballast*, "propose[ ] no workable delineation of what constitutes fact and what constitutes law." 744 F.3d at 1284. Under a deferential regime, district courts would be forced to draw increasingly fine (and ultimately arbitrary) lines between expert opinions of "fact" and "law" in making claim construction determinations. Those lines would then be

redrawn by the Federal Circuit on appeal—*de novo*, since "[i]f a finding designated by the trial judge as one of fact is in reality a conclusion of law, it is freely reviewable." 9C Charles Allen Wright & Arthur R. Miller, *Federal Practice and Procedure* § 2588 & n.10 (3d ed. 2004); *accord id.* § 2579 & n.2 ("An appellate court will regard a finding or conclusion for what it is, regardless of the label the trial court may have put on it."). To avoid such "lengthy peripheral litigation" over what constitutes fact and what law (*Lighting Ballast*, 744 F.3d at 1284), this Court must continue to treat claim construction as "purely legal" in nature. *Markman*, 517 U.S. at 391.

The shifting-standard approach urged by the United States would be equally problematic in practice, requiring district courts and ultimately the Federal Circuit to dissect even particular expert reports into separate law and fact components. Although the government acknowledges that "a district court's ultimate construction of a patent claim remains legal even if the court purports to credit an expert witness's testimony that a skilled artisan would understand the claim in a particular way" (U.S. Br. 23), it also insists that "when a district court based on expert testimony finds that a skilled practitioner would understand a term to have a particular meaning when it is used in the relevant field, the court has made a finding of fact" (*id.* at 22). That is a fine distinction, to say the least, and would prove imperceptible in practice. The government's own application of its standard to this case illustrates the difficulty. The government contends that *one* conclusion that the district court described as "crediting all of [an expert]'s explanation" was factual (*id.* at 31 (punctuation omitted)), but another conclusion purporting to credit the same expert, "though phrased as a credi-

bility finding, is a legal determination" (*id.* at 30). Courts should not be required to make such cuts with the precision of laparoscopic surgery, simply to ensure that some indeterminate subset of the assertions proffered by patent litigants' paid experts will receive deference on appeal.

Deferring to factual findings grounded on expert testimony would generate strong incentives for parties to proffer detailed "expert" reports at the claim-construction phase that simply marshal all of the party's claim-construction arguments in the form of a purported expert opinion regarding how the claim term allegedly would have been understood in the relevant art at the time of the invention. *See* U.S. Br. 22. This sort of process would introduce substantial new expense in a litigation process that *amici* well know is already overly costly. And such testimony is unnecessary to the court, at best: It "amounts to no more than legal opinion—it is precisely the process of construction that the court must undertake." *Markman*, 52 F.3d at 983. A party's expert testimony on claim construction "is no better than opinion testimony on the meaning of statutory terms." *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1585 (Fed. Cir. 1996). At worst, it can be misleading, as "using partisan experts imparts the risk that the experts' testimony will vary the meaning of claim language in favor of their clients." Jennifer Urban, Bell & Howell v. Altek, 14 Berkeley Tech. L.J. 103, 121 (1999).[3]

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[3] Of course, district courts can use *court-appointed* experts or special masters, whose reports will be in the appellate record, regardless of the standard of appellate review. *Contra* Pet. Br. 50–51. Moreover, the Federal Circuit "has a full-time staff of technical advisors to assist the judges with complex matters,

Thus, the possibility of a "battle of experts" is no reason to change the standard of review. *Contra* Pet. Br. 30, 37. Indeed, experts often dispute "ordinary English words given their everyday meanings." Krinsky, *supra*, at 205. And in any event, "any credibility determinations" regarding expert testimony generally will "be subsumed within the necessarily sophisticated analysis of the whole document, required by the standard construction rule that a term can be defined only in a way that comports with the instrument as a whole." *Markman*, 517 U.S. at 389. Thus, mere disputes between experts regarding the proper construction of claim terms cannot justify a departure from *de novo* review. As this Court already has held, "matters of claim construction, *even those aided by expert testimony*, are *questions of law* for the judge." *Id.* at 387 (emphases added; quotation marks omitted).

More generally, *de novo* review does not risk any loss of district court factfinding expertise (*contra* Pet. Br. 18–35), because "claim construction is not a process that normally involves historical facts." *Lighting Ballast*, 744 F.3d at 1293 (Lourie, J., concurring). Allegedly factual material like extrinsic evidence

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and the judges of that court frequently employ law clerks with scientific and technical backgrounds." Lewis A. Kaplan, *Experts in the Courthouse: Problems and Opportunities—Remarks at the Milton Handler Antitrust Review November 29, 2005*, 2006 Colum. Bus. L. Rev. 247, 259 & n.40 (2006). *Contra* Pet. Br. 50 (arguing that "an appellate court's capacity to grapple with scientific and technical questions is much more limited" because district courts can hire "law clerks with specialized training"). This is yet another reason for preserving plenary appellate review of claim construction rather than deferring to the often hurried interpretations of claim language adopted by individual district judges struggling to manage overwhelming caseloads with limited resources.

(Pet. Br. 42–44) is hardly ever dispositive of contested claim constructions, nor should it be. *See* Douglas Y'Barbo, *Is Extrinsic Evidence Ever Necessary to Resolve Claim Construction Disputes?*, 81 J. Pat. & Trademark Off. Soc'y 567, 614–18 (1999). The need for extrinsic evidence, and the frequency with which the appeals court will have a dispositive factual finding to defer to, have been further reduced by *Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) (en banc), which held that "extrinsic evidence in general" merits less weight "than the patent and its prosecution history in determining how to read claim terms."

Because intrinsic evidence is and should be of preeminent value in claim construction, there is little to be gained from deference to district court interpretations of other, less relevant, types of evidence. A "trial judge has no particular advantage over an appellate judge in reviewing this intrinsic evidence, if that is as far as a claim construction inquiry goes; all the evidence is in documentary form and is directly available." Krinsky, *supra*, at 204. The same is true of dictionaries. *Id.* at 207; *see also Cent. States Pension Fund, Se. & Sw. Areas* v. *Indep. Fruit & Produce Co.*, 919 F.2d 1343, 1350 (8th Cir. 1990) ("Recourse to the ordinary, dictionary definition of words is not only reasonable, but may be necessary" in performing "*de novo* review" of the meaning of a collective bargaining agreement); *Teg-Paradigm Envt'l, Inc.* v. *United States*, 465 F.3d 1329, 1336, 1340 (Fed. Cir. 2006) (in a contract interpretation case, reviewing "de novo" a determination based on a dictionary definition); *Avery Dennison Corp.* v. *Allendale Mut. Ins. Co.*, 310 F.3d 1114, 1116 (9th Cir. 2002) (per curiam) (same); *Yockey* v. *Horn*, 880 F.2d 945, 949 (7th Cir. 1989) (same); *Bowers* v. *Baystate Techs., Inc.*,

320 F.3d 1317, 1326 (Fed. Cir. 2003) (independently construing contract terms using non-technical and technical dictionaries).

Because none of the supposed factual components of claim construction is better adjudicated by district courts—and, indeed, the only relevant ones are quintessential legal issues suited for appellate resolution—forcing courts to sunder their claim construction decisions into law and fact would generate less certainty and accuracy but more confusion and litigation than continuing to "treat[ ] interpretative issues as purely legal." *Markman*, 517 U.S. at 391. Thus, "as a matter of the sound administration of justice, one judicial actor"—the Federal Circuit—"is better positioned than another"—the district court—"to decide the issue in question," and so this Court should not "strip" the "federal appellate court of its primary function as an expositor of law." *Miller*, 474 U.S. at 114.

CONCLUSION

For the foregoing reasons, deference to district court claim constructions would undermine important goals, and is irreconcilable with this Court's directives that claim construction presents a question of law and that legal questions must be reviewed *de novo* on appeal. The judgment of the court of appeals should be affirmed.

Respectfully submitted.

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August 18, 2014

AMICUS CURIAE BRIEF

No. 13-854

IN THE

Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., *et al.*,

Petitioners,

v.

SANDOZ, INC., *et al.*,

Respondents.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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INTEREST OF *AMICUS CURIAE*

Amicus curiae Intellectual Property Owners Association (IPO) is a trade association representing companies and individuals in all industries and fields of technology who own or are interested in intellectual property rights.[1] IPO's membership includes more than 200 companies and over 12,000 individuals who are involved in the association either through their companies or as inventor, author, executive, law firm, or attorney member. Founded in 1972, IPO represents the interests of all owners of intellectual property. IPO regularly represents the interests of its members before Congress and the U.S. Patent and Trademark Office and has filed amicus curiae briefs in this Court and other courts on significant issues of intellectual property law. The filing of this brief was approved by the IPO Board of Directors. A list of the IPO board members can be found in the Appendix.[2]

IPO submits this brief in support of a modified standard of appellate review for patent claim construction.

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1. No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than the *Amicus Curiae* or its counsel made a monetary contribution to its preparation or submission. The parties have consented to the filing of this brief.

2. IPO procedures require approval of positions in briefs by a two-thirds majority of directors present and voting.

SUMMARY OF THE ARGUMENT

The Federal Circuit in *Cybor Corp. v. Fas Technologies, Inc.* held that a district court's claim construction, including "any allegedly fact-based questions relating to claim construction," is a pure question of law that is always reviewed *de novo*. 138 F.3d 1448, 1456 (Fed. Cir. 1997). More recently, the Federal Circuit in *Lighting Ballast Control LLC v. Philips Electronics North America Corp.* upheld its decision in *Cybor* on stare decisis grounds. 744 F.3d 1272, 1286 (Fed. Cir. 2014).

This Court made clear in *Markman v. Westview Instruments* that claim construction is a matter "exclusively within the province of the court" while acknowledging that claim construction may involve "evidentiary underpinnings." 517 U.S. 370, 372, 390 (1996). Therefore, the Federal Circuit should continue to treat the ultimate question of what a claim term means as a legal question that is reviewed *de novo* on appeal.

As to the appellate review of evidence that underlies the legal question of claim construction, IPO supports a more nuanced approach. Patent claim interpretation often requires analysis of two evidentiary components: the intrinsic record, i.e., the claims, patent specification, and prosecution history, and extrinsic evidence, such as expert witness testimony. With respect to review of a patent's intrinsic written record, the appellate court sits in exactly the same position as the district court. Appellate judges are just as capable as district court judges of reviewing the language of the claims, the specification, and the prosecution history, and assessing their significance to the ultimate legal conclusion of claim construction.

Therefore, IPO believes that a district court's analysis of claim construction based on the intrinsic record should continue to be reviewed *de novo* by the Federal Circuit

With respect to extrinsic evidence, however, the situation is different. District court judges sit in a better position to weigh the credibility and impact of extrinsic evidence, such as expert testimony, than the appellate court. Therefore, IPO believes that the district court's findings of fact based on properly-considered factual evidence in the extrinsic record should be reviewed under a "clear error" standard in accordance with Federal Rule of Civil Procedure 52(a)(6).

This limited degree of deference to the district court would allow the Federal Circuit to benefit from the district court's superior fact-finding position with respect to extrinsic evidence, while still maintaining consistent application of claim construction law through *de novo* review of the intrinsic record as well as the ultimate legal question of what a claim term means.

ARGUMENT

I. Claim Construction Is a Matter of Law and Should Remain Reviewable *De Novo* by the Federal Circuit

In *Markman v. Westview Instruments*, this Court held that claim construction is a matter "exclusively within the province of the court." 517 U.S. at 372. In so holding, this Court concluded that legal expertise would ensure that the meaning assigned to a claim term will be consistent with the patent's intrinsic record and "preserve the patent's internal coherence." *Id.* at 390. Thus, the IPO

believes that *Cybor*, in holding that the ultimate question of claim construction is a matter of law to be reviewed *de novo*, is consistent with *Markman*.

II. A District Court's Claim Interpretation Relating to the Significance of Statements in the Intrinsic Record Should Remain Reviewable *De Novo* by the Federal Circuit

This Court has also recognized that claim construction may involve "evidentiary underpinnings." *Markman*, 517 U.S. at 390. As noted in *Markman*, courts may be required to resolve issues that "fall somewhere between a pristine legal standard and simple historical fact." *Id.* at 388 (quoting *Miller v. Fenton*, 474 U.S. 104, 114 (1985)). As such, claim construction involves mixed questions of law and fact.

In general, this Court has held that "deferential review of mixed questions of law and fact is warranted when it appears that the district court is 'better positioned' than the appellate court to decide the issue in question or that probing appellate scrutiny will not contribute to the clarity of legal doctrine." *See Salve Regina College v. Russell*, 499 U.S. 225, 233 (1991). With respect to issues on appeal that involve the interpretation of the intrinsic record, however, IPO believes that district court judges are not "better positioned" than the appellate court. Rather, the Federal Circuit sits in exactly the same position as the district court. Importantly, the intrinsic record is both fixed and in writing such that Federal Circuit judges are equally capable of assessing the impact of this evidence on the legal issue of claim construction. Therefore, IPO believes that the district court's analysis of the intrinsic record

should not be accorded deference and should continue to be reviewed *de novo* on appeal.

III. Underlying Factual Determinations Based on Extrinsic Evidence Should be Reviewed For Clear Error by the Federal Circuit

Extrinsic evidence presents a different situation than intrinsic evidence because it is neither fixed in scope nor necessarily in writing. Where the district court hears competing expert testimony, for example, the district court will be in the best position to judge the credibility and impact of any factually disputed evidence.[3] This Court has recognized that district court judges are better positioned to properly consider this evidence and weigh its value in view of the intrinsic record. *See Markman*, 517 U.S. at 390 ("The decisionmaker vested with the task of construing the patent is in the better position to ascertain whether an expert's proposed definition fully comports with the specification and claims and so will preserve the patent's internal coherence."). Therefore, IPO believes that factual findings by the district court

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3. Expert testimony is only one example of extrinsic evidence that underlies the legal claim construction determination. Extrinsic evidence includes anything that is outside of the four-corners of the patent and the prosecution history, such as testimony from inventors and experts, dictionary definitions, and treatises. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005). Extrinsic evidence may be useful "to provide background on the technology at issue, to explain how an invention works, to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Id.* at 1318.

based on extrinsic evidence should be afforded deference on appeal and reviewed under a "clear error" standard. *See* Fed. R. Civ. P. 52(a)(6).

This limited degree of deference should not, however, alter the clear hierarchy of the intrinsic record vis-à-vis extrinsic evidence as set forth in the Federal Circuit's en banc decision in *Phillips v. AWH. See* 415 F.3d 1303, 1318 (Fed. Cir. 2005) ("[E]xtrinsic evidence may be useful to the court, but it is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence."). This hierarchy is consistent with this Court's "standard construction rule that a term can be defined only in a way that comports with the instrument as a whole." *Markman*, 517 U.S. at 389.

This Court explicitly recognized in *Markman* that there will be circumstances in which judges have to make credibility determinations between experts in the course of claim construction, but that those disputes will usually be circumscribed by the intrinsic record.

> It is, of course, true that credibility judgments have to be made about the experts who testify in patent cases, and in theory there could be a case in which a simple credibility judgment would suffice to choose between experts whose testimony was equally consistent with a patent's internal logic. But our own experience with document construction leaves us doubtful that trial courts will run into many cases like that. In the main, we expect, any credibility determinations will be subsumed within the necessarily sophisticated analysis of the

> whole document, required by the standard construction rule that a term can be defined only in a way that comports with the instrument as a whole.

Id. at 389. Thus, while deference should be afforded to extrinsic factual determinations, IPO believes that such facts should remain subsidiary to the intrinsic record for purposes of ultimately assigning meaning to the claim terms.

IV. Maintaining *De Novo* Review by the Federal Circuit of the Intrinsic Record Will Continue to Foster Consistent Claim Construction Rulings

IPO believes that maintaining *de novo* review by the Federal Circuit of the intrinsic record will continue to foster consistent claim construction rulings. Indeed, in deeming all issues of claim construction to be matters for the court in *Markman*, this Court emphasized "the importance of uniformity in the treatment of a given patent." *Markman*, 517 U.S. at 390.

Consistent claim construction rulings are particularly important in instances where the same patent or related patents are litigated before multiple district courts. In addition, consistent application of claim construction jurisprudence is of great value to patent owners and allows them to make informed decisions concerning the scope and value of their own patents and the patents of others. Allowing only limited deference to the district court will permit the Federal Circuit to continue to bring uniformity to claim construction, an issue of central importance in every patent dispute.

CONCLUSION

IPO believes that *Cybor* should be overruled, but only in part. The ultimate conclusion of what a claim term means should remain reviewable *de novo* by the Federal Circuit. In addition, the district court's analysis of the intrinsic record should not be accorded deference and should continue to be reviewed *de novo* on appeal. However, IPO believes that where a district court resolves questions of fact based upon extrinsic evidence, such factual findings should be afforded deference by the Federal Circuit and should be reviewed for clear error. IPO respectfully submits that this framework would continue to promote consistency in claim construction rulings and better align appellate review of claim construction with this Court's precedent and Rule 52(a)(6).

Respectfully submitted,

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APPENDIX

APPENDIX[1]

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AMICUS CURIAE BRIEF

No. 13-854

In The Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC., ET AL.,

Petitioners,

v.

SANDOZ, INC., ET AL.,

Respondents.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

The authors of this brief are law professors who study and teach intellectual property law.

Professor Peter S. Menell holds a law degree and a doctorate degree in economics. Since law school, he has focused a significant portion of his research on intellectual property law. Soon after joining the University of California at Berkeley School of Law faculty in 1990, he laid the groundwork to establish the Berkeley Center for Law & Technology (BCLT). Since its founding in 1995, BCLT has sought to foster the beneficial and ethical understanding of intellectual property (IP) law and related fields as they affect public policy, business, science and technology through a broad range of public policy conferences, collaboration with government agencies (U.S. Patent & Trademark Office, Federal Trade Commission), interaction with intellectual property practitioners and technology companies, and research and educational initiatives. BCLT has provided a valuable

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[1] Pursuant to Sup. Ct. R. 37.6, *amici* note that no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* made a monetary contribution to its preparation or submission. We have received letters from Petitioners and Respondents Sandoz Inc. and Momenta Pharmaceuticals Inc. consenting to the filing of this brief. Respondents Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. have authorized blanket consent with the Clerk's Office.

ongoing vantage point for viewing the evolution of the high technology field as well as the challenges posed by legal protection for computer software for inventors, start-up companies, entrepreneurs, established technology companies, patent professionals, government officials, jurists, and the public. Since 1998, Professor Menell has organized and taught more than 50 judicial education programs for the Federal Judicial Center on intellectual property law, including an annual multi-day program for 30-45 federal judges that covers patent case management with particular attention devoted to claim construction. That experience led him to develop and co-author a treatise for federal judges. *See* Peter S. Menell, Lynn H. Pasahow, James Pooley & Matthew D. Powers, Fed. Judicial Ctr., *Patent Case Management Judicial Guide* (1st ed. 2009, 2d ed. forthcoming (adding Steven C. Carlson and Jeffrey G. Homrig)). From June 2012 through June 2013, Professor Menell served as one of the inaugural Thomas Alva Edison Visiting Professionals at the U.S. Patent & Trademark Office (USPTO) where he devoted a substantial part of his work to improving patent claim clarity. These efforts have informed his research on claim construction jurisprudence and patent case management.

Professor J. Jonas Anderson teaches patent law and trade secret law at American University's Washington College of Law and has also taught intellectual property-related courses at the University of California at Berkeley School of Law. He previously clerked

on the United States Court of Appeals for the Federal Circuit and worked as a patent litigation associate at the Silicon Valley Office of Latham & Watkins. His research has focused on evaluating the institutional design of the patent system and improving the clarity of patent claims.

Professor Arti K. Rai teaches patent law and administrative law at Duke Law School. Professor Rai has also taught intellectual property law at Harvard, Yale, and the University of Pennsylvania law schools. Prior to entering academia, Professor Rai clerked for a trial judge who presided over numerous patent cases in the Northern District of California; worked on patent litigation as an associate at the Washington D.C. office of Jenner & Block; and was a litigation attorney at the U.S. Department of Justice. From 2009 to 2010, Professor Rai served as the Administrator of the Office of External Affairs at the USPTO. As External Affairs Administrator, Professor Rai led the policy analysis of legislation aimed at improving patent quality that ultimately became the America Invents Act of 2011. Professor Rai is also a public member of the Administrative Conference of the United States. Based on this background, Professor Rai is committed to improving judicial and administrative processes in patent law.

SUMMARY OF ARGUMENT

In the seminal *Markman* decision, this Court sought to usher in a more effective, transparent patent litigation regime through its ruling that "the construction of a patent, including terms of art within its claim, is exclusively within the province of the court." *Markman v. Westview Instruments, Inc.* (*Markman II*), 517 U.S. 370, 372 (1996). Notwithstanding the constitutional right to patent jury trials, this Court ruled that claim construction would no longer be conducted by lay jurors in shrouded deliberations. Rather, based on historical analysis of the role of juries in patent cases, characterization of the nature of claim construction, and a comparative assessment of judicial institutional capabilities, this Court concluded that the Seventh Amendment right of trial by jury did not extend to claim construction and that trial judges were better equipped than juries to resolve the mixed fact/law controversies inherent in construing disputed patent claim terms.

In the aftermath of *Markman II*, the Federal Circuit adhered to its *Markman* decision, *Markman v. Westview Instruments, Inc.* (*Markman I*), 52 F.3d 967 (1995) (*en banc*) – that claim construction is a "purely legal issue" subject to plenary *de novo* review, *see Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448, 1451 (Fed. Cir. 1998) (*en banc*) – downplaying this Court's more nuanced description of claim construction as a "mongrel practice" merely "within the province of the court." *Markman II*, 517 U.S. at 372, 378. Over nearly two decades of experience in

the post-*Markman* era, it has become apparent that the Federal Circuit's adherence to its *Markman I* plenary *de novo* appellate review standard has frustrated district courts' distinctive capabilities to apprehend and resolve the factual disputes inherent in claim construction determinations, undermined the transparency of the claim construction process, discouraged detailed and transparent explanations of claim construction reasoning, and produced unusual and at times alarming levels of appellate reversals. These effects have cast doubt on the predictability of patent litigation, discouraged settlements, delayed resolution of patent disputes, and run up the overall costs of patent litigation.

This Court's *Markman II* decision points toward a balanced, structurally sound, legally appropriate, hybrid standard of appellate review that would promote more accurate and efficient patent dispute resolution. Factual determinations underlying claim construction rulings should be subject to the "clearly erroneous" standard of review, while the Federal Circuit should retain *de novo* review over the ultimate claim construction decision. In this manner, district court judges, in their capacity as fact-finders, could better surmount the distinctive challenges posed by the technical, mixed fact/law controversies inherent in patent claim construction. A hybrid standard would encourage district judges to identify the "person of ordinary skill in the art" and, where appropriate, build fuller, more transparent records to support their claim construction decisions. These effects would promote clearer substantive analysis,

more settlements following claim construction and trial, more effective appellate review, and fewer reversals and remands.

A hybrid appellate standard is unlikely to undermine the national uniformity of the patent system. In any event, concerns about national uniformity and clarity of patent claims are more appropriately addressed through improvements to the patent prosecution process, meaningful implementation of the 35 U.S.C. §112(b) claim indefiniteness standard, post-grant review and reexamination procedures, consolidation of claim construction through multi-district litigation, and adjustments to substantive claim construction jurisprudence.

ARGUMENT

I. *Cybor*'s Plenary *De Novo* Standard of Review Misapprehends the Mixed Fact/Law Nature of Patent Claim Construction

It has long been established that district judges must step into the shoes of persons having ordinary skill in the relevant art to resolve disputes as to proper construction of patent claim terms. More than a century ago, Professor William Callyhan Robinson explained that:

> the court may have recourse to any testimony to explain the meaning of its language, or to expert evidence to ascertain the essential characteristics of the described invention

> and the differences between it and other patented inventions, or to papers in the Patent Office which are connected with the patent or whose contents were known to the inventor at the date of his application, to show the significance which he attached to the terms that he employed.

2 WILLIAM CALLYHAN ROBINSON, THE LAW OF PATENTS FOR USEFUL INVENTIONS 248 (1890) (footnote omitted). Robinson further explained that "of whatever aid the courts avail themselves, their interpretation must be based upon the patent as it stands, and when its scope is once fairly apparent it can neither be limited nor extended by extraneous evidence." *Id.*

This same basic framework applies today. Yet the Federal Circuit's *en banc Cybor* ruling, recently reaffirmed in *Lighting Ballast Control LLC v. Philips Electronics North America Corp.*, 744 F.3d 1272 (Fed. Cir. 2014) (*en banc*), holds that patent claim construction is a pure question of law, overriding the more nuanced interplay of documentary sources (the patent record) and historical facts (understandings of skilled artisans).[2]

This Court's *Markman II* decision provides the foundation for resolving this conundrum. In construing the term "inventory" as used in a claim to

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[2] Although Professor Robinson characterized claim construction as a "question of law," it was unclear whether he was referring to the ultimate question. Furthermore, he wrote before the promulgation of FED. R. CIV. P. 52.

a dry-cleaning inventory control system, the jury accepted the patentee expert's testimony regarding the understanding of the term in the art and accordingly found infringement. On post-trial motions, the judge overturned the jury's verdict, explaining that the expert's testimony regarding the definition of "inventory" conflicted with "the ordinary and customary meaning of [this term], as well as the obvious meaning intended by the patentee, determined from the specifications, the drawings and the file histories of the original patent and the patent-in-suit." *Markman v. Westview Instruments, Inc.*, 772 F. Supp. 1535, 1537 (E.D. Pa. 1991).

In upholding the district court's judgment, a majority of the Federal Circuit sitting *en banc* concluded that the construction of patent claims is properly "a matter of law" that should not be given to the jury because of "the fundamental principle of American law that 'the construction of a written evidence is exclusively with the court.'" *Markman I*, 52 F.3d at 978 (citations omitted). Over vehement dissents, the majority concluded that "[b]ecause claim construction is a matter of law, the construction given the claims is reviewed *de novo* on appeal." *Id.* at 979.

Rebuffing the patentee's Seventh Amendment challenge, the majority also masked the inherently factual nature of claim construction by arguing that although the trial judge may use:

> certain extrinsic evidence that the court finds helpful and reject[ ] other evidence as

> unhelpful, and resolv[e] disputes *en route* to pronouncing the meaning of claim language as a matter of law based on the patent documents themselves, the court is *not* crediting certain evidence over other evidence or making factual evidentiary findings. Rather, the court is looking to the extrinsic evidence to assist in its construction of the written document, a task it is required to perform.

Id. at 981 (italics in original) (footnote omitted).

Although this Court affirmed the Federal Circuit's conclusion that the Seventh Amendment did not require that claim construction be resolved by juries, it reached this result through very different reasoning. *See Markman II*, 517 U.S. at 372. Failing to find clear historical evidence of how claim construction was handled in 1791, this Court turned to "the relative interpretive skills of judges and juries and the statutory policies that ought to be furthered by the allocation." *Id.* at 384. The Court came down firmly on the side of allocating claim construction to the trial judge in view of judges' "training in exegesis [of written instruments]," *id.* at 388, notwithstanding what it characterized as the "mongrel practice" of patent claim construction, *id.* at 378. In a critical passage, the Court explained:

> It is, of course, true that credibility judgments have to be made about the experts who testify in patent cases, and in theory there could be a case in which a simple credibility judgment would suffice to choose between experts whose testimony was equally

> consistent with a patent's internal logic. But our own experience with document construction leaves us doubtful that trial courts will run into many cases like that. In the main, we expect, any credibility determinations will be subsumed within the necessarily sophisticated analysis of the whole document, required by the standard construction rule that a term can be defined only in a way that comports with the instrument as a whole. Thus, in these cases a jury's capabilities to evaluate demeanor, to sense the 'mainsprings of human conduct,' or to reflect community standards, are much less significant than a trained ability to evaluate the testimony in relation to the overall structure of the patent. The decisionmaker vested with the task of construing the patent is in the better position to ascertain whether an expert's proposed definition fully comports with the specification and claims and so will preserve the patent's internal coherence. We accordingly think there is sufficient reason to treat construction of terms of art like many other responsibilities that we cede to a judge in the normal course of trial, notwithstanding its evidentiary underpinnings.

Id. at 389-90 (citations omitted).

In contrast with the Federal Circuit's *Markman I* decision, this Court did not deem patent claim construction a "pure question of law." Rather, consistent with its characterization of claim construction as a "mongrel practice," this Court noted merely that

claim construction was a matter "exclusively within the province of the court." *Markman II*, 517 U.S. at 372.

Barely two weeks after the Supreme Court's *Markman II* ruling, a Federal Circuit panel heavily discounted the use of extrinsic evidence, warning that "[a]llowing the public record to be altered or changed by extrinsic evidence introduced at trial, such as expert testimony, would make this right meaningless." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996). In contrast, various other Federal Circuit opinions viewed claim construction as a "mixed question of law and fact" for which fact finding would be set aside only upon a showing of clear error. *See Metaullics Sys. Co. v. Cooper*, 100 F.3d 938 (Fed. Cir. 1996); *Wiener v. NEC Elecs., Inc.*, 102 F.3d 534, 539 (Fed. Cir. 1996) (emphasizing a passage from *Markman II* noting that claim construction "falls somewhere between a pristine legal standard and a simple historical fact").

This split precipitated the Federal Circuit's *en banc* review of the appellate claim construction standard in *Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448 (Fed. Cir. 1998). In a sharply divided decision, the Federal Circuit majority reaffirmed that claim construction is purely a legal issue subject to *de novo* appellate review: "the standard of review in *Markman I* was not changed by the Supreme Court's decision in *Markman II*, and we therefore reaffirm that, as a purely legal question, we review claim construction *de novo* on appeal including any

allegedly fact-based questions relating to claim construction." *Id.* at 1456. The majority downplayed this Court's characterization of claim construction as a "'mongrel practice'" "'falling somewhere between a pristine legal standard and a simple historical fact'" as merely "prefatory comments." *See Cybor*, 138 F.3d at 1455 (quoting *Markman II*, 517 U.S. at 378, 388).

The *Cybor* majority justified plenary *de novo* review on a misapprehension of the block quotation from pages 389-90 of *Markman II* excerpted above. This Court noted that its own "experience with document construction" left it "doubtful" that there would be many cases "in which a simple credibility judgment would suffice to choose between experts whose testimony was equally consistent with a patent's internal logic." *Id.* at 389. It then observed that "[i]n the main, we expect, any credibility determinations will be subsumed within the necessarily sophisticated analysis of the whole document, required by the standard construction rule that a term can be defined only in a way that comports with the instrument as a whole." *Id.* From this inference, this Court reasoned that the trial judge – possessing the

> trained ability to evaluate the testimony in relation to the overall structure of the patent is in the better position to ascertain whether an expert's proposed definition fully comports with the specification and claims and so will preserve the patent's internal coherence. We accordingly think there is sufficient reason to treat construction of terms of

> art like many other responsibilities that we cede to a judge in the normal course of trial, notwithstanding its evidentiary underpinnings.

Id. at 390.

While the sentence noting that "any credibility determinations will be subsumed within the necessarily sophisticated analysis of the whole document" might be read in isolation to downplay the factual underpinnings of claim construction, the following sentence discussing the "many other responsibilities" ceded to the trial judge indicates that this Court intended the opposite. In that sentence, this Court analogized claim construction to rulings that a trial judge routinely resolves during the course of trial – rulings which are not subject to *de novo* review. *See* Steven Alan Childress, *Standards of Review Primer: Federal Civil Appeals*, 229 F.R.D. 267, 289-91 (2005) (observing that "[c]ourts commonly recite the deferential 'abuse of discretion' test as broadly and generally appropriate on review of evidence calls").

That the *Cybor* majority missed this subtlety is apparent in its suggestion that "[n]othing in the Supreme Court's opinion supports the view that the Court endorsed a silent, third option – that claim construction may involve subsidiary or underlying questions of fact." *Cybor*, 138 F.3d at 1455. In the accompanying footnote to this sentence, the *Cybor* majority reasons that "[i]f this were so, surely the Supreme Court would have discussed whether subsidiary or underlying fact questions should be decided

by the judge or the jury." *Id.* at 1455 n.4. This Court's passage quoted above, however, analogizes the trial judge's "trained ability to evaluate the testimony in relation to the overall structure of the patent" to the "many other responsibilities that we cede to a judge in the normal course of trial." *Markman II*, 517 U.S. at 390. In so stating, this Court justifies leaving the entire claim construction exercise in the trial judge's hands "notwithstanding its evidentiary underpinnings" – i.e., its factual character. *See id.* Following this logic, subsidiary factual issues in claim construction rulings, "like the many other responsibilities that we cede to a judge in the normal course of a trial," would be subject to a more deferential standard of review. *See id.*

In this way, *Cybor* overlooked the potential for subsidiary factual questions – such as whether a patent claim term has special meaning to a skilled artisan. Such understanding could well be trumped by the intrinsic record, as occurred in the *Markman* case. Nonetheless, *Cybor*'s rejection of any role for subsidiary fact-finding in claim construction determinations misapprehended essential aspects of the search for patent claim meaning. The Federal Circuit perpetuated this misreading of *Markman II* in its recent ruling upholding the *Cybor de novo* standard on *stare decisis* grounds. *See Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d 1272 (Fed. Cir. 2014) (*en banc*). The dissent in *Lighting Ballast* confronted the appropriate standard of review and concluded that *de novo* review of claim construction rulings "misapprehends the Supreme

Court's guidance, contravenes the Federal Rules of Civil Procedure, and adds considerable uncertainty and expense to patent litigation." *See id.* at 1297 (O'Malley, J., dissenting).

II. The Post-*Markman* Era Has Revealed Serious Failings of Plenary *De Novo* Review of Claim Construction Rulings

Over the nearly two decades since the *Markman* decisions, it has become apparent that the Federal Circuit's adherence to its *Markman I* appellate standard has frustrated district judges' distinctive capabilities to apprehend and resolve the factual disputes underlying claim construction determinations, undermined the transparency of the claim construction process, discouraged detailed and transparent explanations of claim construction reasoning, and produced unusual and at times alarming levels of appellate reversals.

Following *Markman*, trial judges initially sought to apply their experience gathering and weighing evidence, including expert testimony, to this challenging new responsibility. While properly emphasizing the primacy of intrinsic evidence to claim construction, the *Vitronics/Cybor* line of cases unfortunately steered district judges away from learning from skilled artisans and using evidentiary techniques for resolving disputes among purported experts. An unusually high reversal rate for claim construction rulings following the *Cybor* decision signaled dissensus.

See Kimberly A. Moore, Markman *Eight Years Later: Is Claim Construction More Predictable?*, 9 LEWIS & CLARK L. REV. 231, 232-34 (2005). The *de novo* standard severely constrained, if not effectively deprived, district judges of resort to an essential tool – focused evidentiary hearings – for resolving disputes over the meaning of scientific and technological terms. With rare exception, federal district judges lack science or engineering training. *See* S. Jay Plager, *Abolish the Court of Federal Claims? A Question of Democratic Principle*, 71 GEO. WASH. L. REV. 791, 797 (2003) (observing that "[m]ost district court judges do not have scientific training, and most have not chosen law clerks with technical or patent backgrounds"). Yet claim construction doctrine demands that judges interpret patent claims from the standpoint of "persons having ordinary skill in the art."

Although *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*), afforded trial judges greater leeway to gather extrinsic evidence, district judges have long since abandoned formal evidentiary proceedings as part of the claim construction process and steered clear of explaining claim construction rulings as based on any fact-finding. In research examining the effect of the *Phillips* decision on reversal rates and other aspects of patent claim construction, two of us found that the reversal rate for claim construction appeals has declined in the past decade. *See* Jonas Anderson & Peter S. Menell, *Informal Deference: A Historical, Empirical, and Normative Analysis of Patent Claim Construction*, 108 Nw. U. L. Rev. 1

(2013). Our research indicates, however, that the decline can be attributed to informal deference rather than improved fact-finding or more transparency in the decision-making process. The shadow of formal *de novo* review continues to cast doubt on the predictability of patent litigation, discourage settlements following claim construction and trial, delay resolution of patent disputes, and run up the overall costs of patent litigation. Although informal deference may well be an improvement over pure *de novo* review, it falls short of the proper division of responsibility between district and appellate courts and represents at best an entirely discretionary and panel-dependent regime.

More fundamentally, the *Cybor* majority's failure to acknowledge the role for fact-finding deprives the patent adjudication system of the evidentiary record and systematic analysis essential to sound administration of justice. Because of the *de novo* standard, district judges lack motivation to delve beyond the intrinsic record. In fact, as this case illustrates, litigants risk reversal on appeal to the extent that they persuade a judge to rely upon extrinsic evidence. Furthermore, trial judges appropriately perceive that relying on extrinsic evidence in their claim construction ruling could be grounds for reversal. As a result, the skilled artisan's perspective is rarely reflected in trial judges' *Markman* rulings. For this reason, the Federal Circuit makes nearly all of its claim construction decisions without reference to the skilled artisan's perspective. *See* Anderson & Menell, *supra*, at 5

(finding that only 13 of the 778 (1.7%) claim construction appellate opinions issued from 2000 to 2010 even identify the applicable skilled artisan).

In addition to compromising the care and logic that comes from building a detailed factual record and preparing a reasoned opinion, the plenary *de novo* review regime undermines the appellate process. The parties, the public, and the appellate court lack the fully developed record and reasoned opinions that would enable them to know all of the relevant input and what influenced the trial judge's decision. Instead, plenary *de novo* review substitutes independent review of an anemic record – typically limited to the intrinsic evidence. *See* Anderson & Menell, *supra*, at 45 (finding that in construing claim terms, the Federal Circuit has consulted extrinsic sources only 26.3% of the time since 2005).

The private and social costs of the plenary *de novo* standard of review include lower quality decision-making at both the trial and appellate levels, higher costs of litigation as a result of more appeals and retrials following reversals, greater litigation uncertainty, longer case pendency and litigation costs as a result of fewer and delayed settlements, the distraction and disruption of litigation on the technology marketplace, and the added burdens on the particular judges and the larger judicial system.

Many of these costs derive from the discouraging effect of plenary *de novo* review on early settlement of

patent cases. The cost of an appeal typically pales in comparison to the costs of litigating a patent case through trial. Consequently, parties who lose at trial are more likely to pursue an appeal under the plenary *de novo* standard than they would under a more deferential regime. This not only delays resolution, but also results in a substantial number of retrials. Overall, the plenary *de novo* standard has raised the cost of patent litigation without any discernible benefits in terms of improved decision-making.

III. A Hybrid Appellate Review Standard for Claim Construction Rulings

Federal Rule of Civil Procedure 52(a)(6) provides that "[f]indings of fact, whether based on oral or other evidence, must not be set aside unless clearly erroneous, and the reviewing court must give due regard to the trial court's opportunity to judge the witnesses' credibility." *See Anderson v. City of Bessemer City*, 470 U.S. 564, 574-75 (1985).

Thus, the Federal Circuit must defer to trial judges' factual determinations in claim construction rulings. Since the patent document defines the invention, the Federal Circuit retains a substantial check on the overall claim construction determination through *de novo* authority over the intrinsic record and over whether a trial court's factual finding contradicts limitations on the the patent's scope reflected in the intrinsic evidence – the patent document and file wrapper.

The basis for "deferring" to lower court claim constructions is not trial judges' policy expertise or experience vis-à-vis the Federal Circuit but rather the inherently factual aspects of some parts of patent claim construction – in particular, the meaning of a contested claim term from the perspective of a skilled artisan at a particular moment in time. The mongrel character of patent claim construction indicates that a reviewing court should be cautious in overturning a district court's well-supported claim construction absent clear intrinsic evidence to the contrary. Unlike a statute (which is viewed from a lay perspective), the intrinsic evidence in a patent case is viewed from the standpoint of a skilled artisan.

The process of understanding this standpoint should begin, as current claim construction practice does, with the trial judge attempting to determine the plain and ordinary meaning of the patent claim terms within the context of the claim. The trial judge should then determine whether the claim term has particular meaning based on its usage in the patent specification, technical art, and/or claim drafting convention. *Cf.* John M. Golden, *Construing Patent Claims According to Their "Interpretive Community": A Call for an Attorney-Plus-Artisan Perspective*, 21 HARV. J.L. & TECH. 321, 348-62 (2008). The more deferential standard of appellate review would invigorate trial courts' development of the factual record. Although this standard could produce "battles of the experts," it should not do so any more in claim construction cases than it does in other areas in which

courts must view documents or other evidence from a specialized standpoint.

Furthermore, hybrid standards are already pervasive in patent law. For example, as this Court has long recognized, the pivotal patent validity doctrine of nonobviousness requires the trial court to make factual findings that underpin the ultimate legal conclusion. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 426-27 (2007); *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Moreover, as this Court has emphasized, the Federal Circuit must follow ordinary legal rules by reviewing factual findings under the deferential standard of Rule 52(a). *See Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 810-11 (1986) (*per curiam*).

It is important for trial judges to incorporate into their analysis the overarching notice goal of the patent system. As Professor Robinson explained more than a century ago, intrinsic evidence should play a central and critical role in claim construction. But courts should not be constrained in their use of expert witnesses in determining the manner in which a patent would be interpreted by one of ordinary skill in the art. Indeed, in some cases, it may be impossible to interpret a claim correctly without the assistance of experts in the relevant field.

In practice, this proposed standard of review, consistent with *Markman II*, will introduce a hybrid character to appellate review depending on the quality of the patent disclosure, nature of the disputed

claim term (technical, common parlance, or glossary), evidentiary record, and the rationale for the trial court's construction. Where the patent clearly defines the disputed term, there will be little or no role for extrinsic evidence or fact-finding. But where the patent instrument is opaque, the specification does not address the term (as occurs with some frequency when claims are amended), or the term arguably diverges from common parlance, then the judge's resolution of conflicting testimony takes on much greater moment.

Such an approach comports with Federal Rule of Civil Procedure 52(a) and mirrors the general framework in which district judges operate. Over time, the district courts will likely better account for the fact/law distinction in their Patent Local Rules and *Markman* hearings. For example, courts could require litigants to more clearly set forth the intrinsic and extrinsic bases for claim construction, requiring a party seeking to bring forward expert testimony to disclose any gaps in the intrinsic record that skilled artisan testimony could fill. Furthermore, courts could innovate in the use of focused evidentiary hearings, possibly in conjunction with tutorials, for efficiently developing a factual record for claim construction.

IV. The Hybrid Appellate Review Standard, "National Uniformity," and the Role of the USPTO

The Federal Circuit based its plenary *de novo* standard in part on promoting better notice, certainty, and national uniformity of patent boundaries. The logic appears to be that as the national appellate patent court, the Federal Circuit is uniquely positioned to provide nationally uniform interpretations of patent boundaries. While these are worthy goals, it is doubtful that plenary *de novo* review of claim construction rulings can ever serve these goals effectively due to structural and practical problems.

At the structural level, courts lack authority to declare the boundaries of a patent beyond the parties in suit. *See Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found.*, 402 U.S. 313 (1971). Thus, the Federal Circuit's interpretation of a patent in one case cannot be asserted offensively by the patentee in a later infringement action against other defendants. At most, it can bar the patentee from seeking an alternative interpretation. Because the patent system has no mechanism for conclusively establishing patent scope with regard to all potential infringers, the certainty that flows from appellate interpretations is not ironclad, as subsequent defendants can potentially bring new evidence or more effective advocacy to bear on claim meaning. While plenary *de novo* review increases the likelihood that the Federal Circuit will construe a patent in the same manner across cases, it also decreases certainty by making district court

claim constructions more vulnerable to reversal. *See* Kelly Casey Mullally, *Legal (Un)Certainty, Legal Process, and Patent Law*, 43 LOY. L.A. L. REV. 1109 (2010).

If the Federal Circuit's construction of a term in a particular patent claim cannot bind even subsequent defendants against whom that patent claim term is asserted, it can hardly create any binding guidance for litigation of third-party patents that happen to use the same term. Indeed, given the variability of patent claim terms, and the fact that terms must be construed in light of the specification and other intrinsic evidence, even the precedential value of a given construction is likely to be limited. Precedential value is likely to arise not from any conclusion the Federal Circuit reaches about a particular term but rather from generalizable rules it applies in reaching that conclusion. *See* Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1086-87 (2003). With respect to those generalizable rules, which represent the pivotal components of a nationally uniform patent system, our proposed hybrid standard would mandate *de novo* review.

At a more practical level, the sheer number of patents (and patent claims) issued annually by the Patent Office severely limits the Federal Circuit's ability to provide more than a thimble-sized solution to an ocean-sized challenge. The Federal Circuit is able to review a very small subset of the millions of patent claims granted each year, and this review

occurs only after years of litigation and typically millions of dollars spent on litigation.

Concerns about the clarity of patent claims are more appropriately addressed through improvements to the patent prosecution process, post-grant review and reexamination, consolidation of claim construction through multi-district litigation, and adjustments to substantive claim construction jurisprudence. The Patent Office should play a more central role in achieving clear patent boundaries at the front end and developing taxonomies, search tools, and other mechanisms for reinvigorating the patent system's role in resource planning. *See generally* Peter S. Menell & Michael J. Meurer, *Notice Failure and Notice Externalities*, 5 J. LEGAL ANALYSIS 1 (2013). This Court's decision in *Nautilus, Inc. v. Biosig Instruments, Inc.*, No. 13-369, 2014 WL 2440536 (June 2, 2014) encourages patent applicants and the USPTO to place greater emphasis on patent claim clarity.

The Patent Office should impose greater responsibility on patentees to delineate their claims at the front end of the patent process by requiring applicants to: (1) set forth their claims in a standardized, detailed format that delineates each claim restriction in a separate field; (2) specifically define any potentially ambiguous claim terms – including terms of degree (such as "approximately," "substantially"); (3) designate a default dictionary for guiding the interpretation of any undefined claim terms; (4) hyperlink to or otherwise specify the corresponding "structure, material, or acts" in means-plus-function claim

elements; and (5) consent to recordation of interviews. *See* Peter S. Menell, *Promoting Patent Claim Clarity* (Nov. 1, 2012), http://papers.ssrn.com/sol3/papers.cfm?abstract_id= 2171287; Peter S. Menell, *It's Time to Make Vague Software Patents More Clear*, WIRED (Feb. 7, 2013), http://www.wired.com/opinion/2013/02/its-time-to-make-vague-software-patents-more-clear/. The dispute over the meaning of the claim term in this case (as well as the many other cases, including *Phillips,* dealing with the presumption that a claim is governed by 35 U.S.C. §112(f)) could likely have been avoided if the USPTO required applicants to simply check a box to indicate whether or not they intended to invoke 35 U.S.C. §112(f). The court can encourage such policies more generally by developing a *contra proferentem* (interpretation against the draftsperson) principle for claim construction.

The past decade has revealed that the Patent Office's lax review of claim boundaries is penny-wise and pound-foolish. Failure to scrutinize claim language at the front end of the patent system causes far more harm than good, even if only a small percentage of patents are litigated. It has led to proliferation of poorly drafted patent claims, which contributes to reckless patent assertion, complicates technology licensing, fuels uncertainty in patent litigation, and runs up the litigation and social costs of the patent system.

The Patent Office is paying greater attention to problems of patent notice. It has implemented guidelines for patent examiners that appear to be

increasing rejections of unclear or poorly drafted claims and it is systematically engaging stakeholders in discussions of what other actions it can take. The USPTO is also making vigorous use of the new post-grant review powers under the America Invents Act. Arti K. Rai, *Improving (Software) Patent Quality Through the Administrative Process*, 51 HOUS. L. REV. 503 (2013).

To be sure, much remains to be done. It is unrealistic, however, to believe that courts can make a dent in the patent notice problem through plenary *de novo* review. To the contrary, such a standard undermines the development of an informed record and cannot override the established legal principles and a formal rule, FED. R. CIV. P. 52(a)(6), supporting measured deference to subsidiary factual determinations.

CONCLUSION

A hybrid standard of appellate review of claim construction rulings would leverage district court judges' special ability to develop the evidentiary record required to resolve the mixed fact/law controversies inherent in patent claim construction while enhancing the quality of appellate review. According greater deference to trial courts through clear error review of the factual underpinnings of claim construction rulings that are supported by sound evidentiary processes, properly documented records, and transparent reasoning would promote more systematic,

well-founded claim construction analysis. Combining deferential review of factual findings with *de novo* review of the overarching claim construction determination – focused on ensuring that claim construction comported with the intrinsic evidence and on ensuring that the trial court followed generally applicable rules of claim construction – would provide the appropriate appellate safeguard.

Respectfully submitted,

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